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Hypermobility syndrome and its connection with nerve entrapment syndromes, the example of the thoracic outlet syndrome

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ABSTRACT

Background: Since its first mention by Kirk et al. in 1967 and its recognition as a full-fledged rheumatologic disorder, the hypermobility syndrome (HMS) has been increasingly investigated and reported in the scientific literature. Expeditiously renamed benign joint hypermobility syndrome in the patent absence of life-threatening complications, its relatively innocuous character has been progressively reconsidered. In fact, the HMS tends to date to be considered analogous to the Ehlers-Danlos syndrome-hypermobility type, a heritable disease of connective tissue, and therefore emerges as a chiefly rheumatologic disorder with possible widespread reverberations in practically all organs and systems. The condition thence goes beyond the sole involvement of the musculoskeletal system and is recurrently associated with seemingly-unrelated and more or less severe conditions (cardiovascular, pulmonary, gastro-intestinal…). However, neurologic implications of the hypermobility syndrome remain poorly documented, particularly those regarding the peripheral nervous system. Ranking amongst the afflictions of the latter, nerve entrapment syndromes (NES) comprehend a multitude of categories, notably the thoracic outlet syndrome (TOS). And if their pathological mechanisms are generally apprehended (entrapment neuropathies result from focal lesions of a peripheral nerve at vulnerable anatomical sites), their aetiology often remain obscure.

Methods: The present work is a literary review analyzing trials, reviews and books about hypermobility syndrome on one hand, and entrapment neuropathies _with a focus on the thoracic outlet syndrome_ on the other hand. It aims at thoroughly describing both conditions, outlining their connectedness and the impact this connectedness could have on the management of the thoracic outlet syndrome. Information and data sources were retrieved from English and French publications, released between 1967 and 2013, using electronic databases and reference lists of articles. PeDro, PubMed, ScienceDirect and Cochrane library were inquired using the following key words: nerve entrapment, compression neuropathy, tunnel syndrome, canal syndrome, outlet syndrome, rehabilitation, physical therapy, physiotherapy, hypermobility, hyperlaxity and double-jointed. A restriction for the type of publication (meta-analysis, systematic review,

review, clinical trials, comparative trials, practice guidelines and case studies) was applied when allowed by the databases' research tools.

Research questions:

- Is HMS associated with the onset of NESs, and more specifically with the thoracic outlet syndrome ?
- If so, by which pathological mechanisms ?
- If so, could it impact the therapeutic management of NESs and, more specifically, of the thoracic outlet syndrome ?

Findings: The literature linking NES to HMS is very scarce. However, in the few studies retrieved, rates of incidence of some types of NES (carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome, digital nerve compression, sciatica, common peroneal nerve palsy) have been found to be higher in hypermobile patients. As a consequence, hypermobility is though to constitute a predisposing/causative factor in their onset. The pathological mechanisms for the onset of NES within the framework of a pre-existing HMS are poorly documented. The very structure of peripheral nerves could be altered in their protective connective tissue components, rendering the peripheral nervous tissue more prone to injury; also, because of the static and dynamic postural impairment which is seen in HMS, mechanical forces exerted on the peripheral nervous system could exceed the resistive properties of already defective connective tissues. Finally orthopaedic deformities commonly seen in HMS could enhance the promiscuity of the nerve with its surroundings. It appears that, because of its pathological features, but also because of its under-recognition HMS could negatively impact the management which is done of some types of NES; first on the surgical level, for non-conservative approach is often ineffective in HMS suffers and for scarring can be impaired. On a pharmacotherapeutic standpoint, some typical strategies proposed for the treatment of NES could be either inefficient, or worse, have counter-productive effects. Documentation on the physiotherapeutic management of NES within the framework of hypermobility is practically inexistent. One study however demonstrated that in the case of the thoracic outlet syndrome, hypermobility was a predictive factor of negative prognosis.

Conclusion: HMS and the aforementioned NESs are undeniably connected. Because of its suspected high prevalence amongst rheumatology patients and of its almost ubiquitous ability to trigger musculoskeletal pathologies, it appears that hypermobility should be looked for as a rule in patients presenting these NESs. An educated guess would be that outcomes of their overall management would be enhanced by a better selection of the therapeutic strategies, hence a sharper tailoring of their management. However this hypothesis, as many other aspects of HMS firstly, and secondarily of the connection between NESs and HMS, remains to be investigated. The probably most highly anticipated advance in the field of HMS-related researches is the discovery of its underlying genetic defect, which would allow solving a majority if the conundrums arouse by this disorder.

Key words: Hypermobility, Hypermobility syndrome, Entrapment neuropathy, Thoracic outlet syndrome, Connective tissue, Peripheral nerve, Management.

ABSTRAKT

Úvod: Od chvíle kdy se o něm v roce 1967 poprvé zmínili Kirk a spol. a kdy pak byl uznán za plně rozvinutou revmatologickou poruchu, je hypermobilní syndrom (HMS) stále častěji zkoumán a popisován v odborné literatuře. Poté co byl pro zjevnou nepřítomnost život ohrožujících komplikací spěšně přejmenován na syndrom benigní kloubní hypermobility, je jeho poměrně neškodná povaha studována s rostoucím zájmem. Ba co více, HMS se do dnešních dnů považuje za obdobu Ehlers-Danlosova syndromu hypermobilního typu, což je dědičné onemocnění pojivové tkáně, a z toho důvodu se vyskytuje především jako revmatologická porucha s potenciálně rozsáhlým postižením prakticky všech orgánů a systémů. Tento stav tudíž přesahuje hranice onemocnění výlučně muskuloskeletálního systému a vyskytuje se opakovaně v souvislosti s více či méně závažnými chorobami, ke kterým zdánlivě nemá žádný vztah (kardiovaskulárními, plicními, gastrointestinálními .....). Přesto ale zůstávají chabě dokumentovány neurologické implikace hypermobilního syndromu, zejména ty, které se týkají periferní nervové soustavy. Pokud jde o postižení právě v této oblasti, zahrnují syndromy uskřinutého nervu (NES – nerve entrapment syndrome) celou řadu kategorií, a to zvláště syndrom horní hrudní apertury. A třebaže jejich patologické mechanismy už byly celkem vzato pochopeny (uskřinutí vzniká v důsledku fokálních lézí periferního nervu na zranitelných anatomických místech), jejich původ zůstává často neobjasněn.

Metodika: Tato práce je literární přehled analyzující klinické pokusy, recenze a knihy o hypermobilním syndromu na jedné straně, a o neuropatiích z uskřinutí se zvláštním zřetelem na syndrom horní hrudní apertury na straně druhé. Klade si za cíl důkladně oba syndromy popsat, ukázat v hlavních rysech jejich souvislosti i důsledky, které by tyto souvislosti mohly mít pro management syndromu horní hrudní apertury. Zdroje informací a údajů byly převzaty z anglických a francouzských publikací vydaných mezi roky 1967 a 2013 a z elektronických databází a referenčních seznamů článků. Pro použití dále uvedených klíčových slov byly konzultovány zdroje jako PeDro, PubMed, ScienceDirect a Cochrane Library: uskřinutí nervu, kompresivní neuropatie, syndrom tunelu, syndrom kanálu, syndrom apertury, rehabilitace, fyzikální terapie, fyzioterapie, hypermobilita, hyperlaxita, dvoukloubový. Pokud to vyhledávací nástroje databází

dovolily, byla uplatněna omezení co do typu publikací (metaanalýza, systematický přehled, recenze, klinické pokusy, srovnávací pokusy, praktické směrnice a kazuistiky).

Výzkumné otázky:

- Souvisí hypermobilní syndrom s nástupem syndromu uskřinutého nervu, konkrétně se syndromem horní hrudní apertury?

- Pokud ano, jaké patologické mechanismy se tu uplatňují?

- Pokud ano, mohlo by to mít vliv na terapeutický přístup k syndromu uskřinutého nervu, konkrétně k syndromu horní hrudní apertury?

Výsledky: Literatury spojující syndrom uskřinutého nervu s hypermobilním syndromem je poskrovnu. Nicméně, z onoho mála nalezených studií vyplývá, že některé typy syndromu uskřinutého nervu (syndrom karpálního tunelu, syndrom tarzálního tunelu, syndrom horní hrudní apertury, komprese digitálního nervu, ischias, paréza společného peroneálního nervu) se častěji vyskytují u hypermobilních pacientů. Z toho důvodu se má za to, že hypermobilita působí jako predisponující/příčinný faktor při jejich vzniku. Málo jsou doloženy patologické mechanismy rozvoje syndromu uskřinutého nervu u již existující hypermobility. Sama struktura periferních nervů by se mohla změnit co do složek ochranného pojiva a tak učinit periferní nervovou tkáň ještě náchylnější k poranění; a to i z toho důvodu, že pro statické i dynamické posturální zhoršení zjišťované u hypermobilního syndromu by mechanické síly působící na periferní nervovou soustavu mohly překonat odolnost už tak postižených pojivových tkání. Nakonec by ortopedické deformity, jak je u HMS často vídáme, mohly zvýraznit promíšenost nervu s jeho okolím. Zdá se, že pro jeho patologické rysy, ale také proto, že je nedostatečně rozpoznáván, by HMS mohl mít negativní dopad na ošetřování, které se u některých typů NES uplatňuje; a to především na chirurgické úrovni vzhledem k tomu, že nekonzervativní řešení je u pacientů s HMS často neúčinné a že může narušit jizvení. Z farmakoterapeutického hlediska mohou být některé typické strategie uvažované pro léčbu NES buď neúčinné anebo, v horším případě, mít kontraproduktivní účinky. Doklady o fyzioterapeutickém řešení syndromu uskřinutého nervu v rámci hypermobility prakticky neexistují. Přesto však jedna studie ukázala, že v případě

syndromu horní hrudní apertury byla hypermobilita jedním z prediktivních faktorů negativní prognózy.

Závěr: Hypermobilní syndrom a již uvedený syndrom uskřinutého nervu spolu nepopiratelně souvisejí. Vzhledem k jeho předpokládané vysoké prevalenci mezi revmatologickými pacienty a k jeho téměř všudypřítomné schopnosti vyvolat muskuloskeletální poruchy se zdá, že hypermobilitu lze u pacientů s příznaky takových uskřinutí brát jako pravidlo. Poučeným odhadem by pak bylo, že výsledkům jejich celkového řešení by prospěl lepší výběr léčebných strategií a z toho důvodu také individuálnější úprava léčby. Zbývá však ještě přezkoumat především tuto hypotézu a mnoho dalších aspektů HMS a, zadruhé, souvislost mezi NES a HMS. Za pravděpodobně nejvíce očekávaný pokrok na poli výzkumu HMS se pokládá objev zásadního genetického defektu, který by umožnil vyřešit většinu hádanek vyvolávaných touto poruchou.

Klíčová slova: Hypermobilita, Hypermobilní syndrom, Neuropatie z uskřinutí, Syndrom horní hrudní apertury, Pojivová tkáň, Periferní nerv, Management

☙ DECLARATION ❧

I hereby declare that I worked on this thesis separately, under the guidance of a consultant, Doc., PaedDr. Dagmar Pavlů. I used only cited professional and literary sources. No information has been misused and all were authorized and adequately documented.

ACKNOWLEDGEMENTS

The inspiration for the topic of this thesis originates from a rather distressing personal experience: the diagnosis of a Paget-Schroetter syndrome made on my twin sister in her early twenties. Retrospectively, the failure of the conservative strategy she bilaterally underwent and my own experience of successful conservative management as a TOS patient piqued my curiosity of budding physiotherapist. In this regard, this thesis is largely dedicated to her.

On a lighter tone, I would like to thank these fellow thesis writers (current or former) and these others who practice professions resolutely detached from the medical field but still endeavoured to understand at least the general topic of this thesis: my partner, my family, and my friends. Michael, Linda, Maman, Papa, Lousin, Farah, Trisita, Umit, Hannah,… through your presence or emails, phone calls, visits and even parcels, you also managed to keep up my spirits, shared the load of stress with me and more than once aptly advised me. In particular my mother for her constant attention and my partner, although the latter is the one to "blame" for my reenlisting in a master degree, both of you now know more than ever what an emotional rollercoaster can the writing of a thesis be and yet still managed to take the edge of it for me.

In like manner, I am extremely grateful to my thesis supervisor, Docentka Dagmar Pavlu, for she's always made herself available for me and remained attentive to my manifold interrogations. Particularly at the end of this project, she gave me of her time and energy until the very last minutes. More generally, I thank her for the excellence of her teaching, of the knowledge she shared with me and my classmates and for the scientific rigor which she steadily showed in her classes.

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1. Introduction

Joint hypermobility, as a distinctive feature of heritable disorders of connective tissue (HDCT), under its pathological presentation commonly termed as "hypermobility syndrome" (HMS), "joint hypermobility syndrome" (JHS) or "benign joint hypermobility syndrome" (BJHS), constitutes a intricate and multifaceted clinical entity[1]. It chiefly refers to an either silent or symptomatic (hence the denomination "syndrome" or not) hyperlaxity of multiple joints, namely an increased looseness of articular structures, whether it is generalized or not[2]. Over the past decades, joint hypermobility has been increasingly reported amongst the scientific literature, notably under the suspicion of constituting, either a non-causative associated feature or participating factor into a variety of other non-rheumatologic disorders, sometimes termed as "extra-articular manifestations"[2,3]. Moreover, its prevalence in the adult population, although unequivocally recognized for significantly varying with age, gender and race, seem to be currently revised upwards[4], and experience proves that, for the physical therapy practitioner, it is not uncommon to encounter patients presenting a certain degree of hyperlaxity in several joints.

On the other hand, nerve entrapment syndromes (NES)*, namely the focal compressions of peripheral nerves at a vulnerable anatomical sites[5], encompass a wide range of conditions. With varying prevalences amongst the adult population and varying distribution of symptoms according to the nerve which is affected, we list about 50 different types[6] of entrapment neuropathies. And if the carpal tunnel syndrome (CTS) is unquestionably the "star" of nerve entrapments, other less famous _and sometimes more controversial as the thoracic outlet syndrome (TOS)_ compression neuropathies are frequently encountered in physiotherapy practices. And because of their analogous pathological presentation (sensory/motor/autonomic impairment along a peripheral nerve distribution), their treatment aims remain closely related. Yet, if the pathological mechanisms involved in the development of nerve entrapment-related symptoms is to date broadly understood, their exact aetiology is often only partially apprehended. By contrast, a series of risk factor _notably occupational and ergonomical_ for the onset of these disorders have been put forward.

* Also known as entrapment neuroapthies, compression neuropathies, nerve compression syndromes, tunnel syndromes, canal syndromes, outlet syndromes

Having been physiotherapeutically treated for a TOS, both I and my twin sister, but with markedly different outcomes, and both of us presenting hypermobility (yet only I was also diagnosed with the latter), I cannot help but question about the clinical management which is done of these syndromes. Yet for mild and moderate forms of nerve entrapments and postoperatively, physical therapy constitutes a mostly appraised form of treatment. Could it be that risk factors were sensibly different in our cases ? Or rather, are we, physiotherapists, and more globally care givers, missing something when a patient with an entrapment neuropathy is addressed to us ? Could hypermobility, in the absence of other underlying musculoskeletal disorders, be the missing link, or a factor of poor outcomes ?

Few publications mention the link between compression neuropathies and an underlying hypermobility (now widely acknowledged as a heritable disorder of connective tissues (HDCT[7]) and the outcomes of treatments. Taking the thoracic outlet syndrome as an example of NES, this thesis proposes therefore to present the actual knowledge on first the joint hypermobility (both as a clinical feature and a syndrome) and secondarily on compression neuropathies with a focus on the TOS; Also, and along a more practical view, an attempt will be done to put into perspective the still existing shortcomings regarding their comprehension. In a synthetic part, entitled findings, data and evidence gathered about both syndromes will be summarised. A review of their to-date established connection, will be provided, focussing on the underlying pathological mechanisms in play and their potential mutual influence in term of therapeutic management. These findings will be then discussed regarding their level of evidence and will be put in perspective in a subjective manner. In a conclusive part, the actual state of research regarding HMS will be discussed and trails of investigation will be considered.

2. Objectives and research methods

This thesis is a literary review analyzing trials, reviews and books on hypermobility and entrapment neuropathies in general and with a focus on the thoracic outlet syndrome. Information and data sources were retrieved between Winter 2011 and Summer 2013, from English and French publications released between 1967 and 2012, using electronic databases and reference lists of articles. A restriction for the type of publication (meta-analysis, systematic review, review, clinical trials, comparative trials, practice guidelines and case reports) was applied when allowed by the databases' research tools.

PeDro, PubMed, ScienceDirect and Cochrane library were investigated using a set of key words remaining voluntarily generalist (due to the wide range of compression neuropathies and the variety of terms designating hypermobility of joints) with 3 main occurrences and their synonyms, as listed below.

- hypermobility / hyperlaxity / double-jointed
- nerve entrapment / compression neuropathy / tunnel syndrome / canal syndrome / outlet syndrome / space syndrome
- physical therapy / physiotherapy / rehabilitation / conservative

Additionnally and when possible, research by title, keywords and abstracts and combinations of key-words have been performed:

- (hypermobility OR hyperlaxity OR double-jointed) AND (nerve entrapment OR compression neuropathy OR tunnel syndrome OR canal syndrome OR outlet syndrome OR space syndrome)
- (physical therapy OR physiotherapy OR rehabilitation OR conservative) AND (hypermobility OR hyperlaxity OR double-jointed)
- (physical therapy OR physiotherapy OR rehabilitation OR conservative) AND (nerve entrapment OR compression neuropathy OR tunnel syndrome OR canal syndrome OR outlet syndrome OR space syndrome)

Sources have then been reviewed by their abstracts and selected or dismissed according to the following inclusion and exclusion criteria :

- Inclusion criteria:
    - type of publication: meta-analysis, systematic review, review, clinical trials, comparative trials, practice guidelines and case reports
    - language of publication : French or English
    - pathology: nerve entrapment syndromes
    - pathology: joint hypermobility, joint hypermobility syndrome, hypermobility syndrome, benign joint hypermobility syndrome, Ehlers-Danlos syndrome hypermobility type.
- Exclusion criteria:
    - population: children
    - pathology: nerve entrapment syndromes of the lower extremities
    - pathology: traumatic injury to peripheral nerves, polyneuropathies, multiple mononeuropathies
    - pathology: other heritable connective tissue disorder than hypermobility or Ehlers-Danlos syndrome when the hypermobility type is not specified
    - pathology: focal hypermobility
    - date of publication: prior to 1967 for hypermobility

Additional sources, using reference lists of retrieved articles and using the same inclusion and exclusion criteria have be en in addition selected to complement the theoretical basis of this work.

The objectives of this thesis being to first outline the connectedness of joint hypermobility and nerve compression syndromes, it seemed of peculiar importance to exhaustively review both conditions. In order to provide the reader with up-to-date knowledge, meta-analysis, systematic review and practice guidelines, but also case studies, clinical trials and comparative trials have mostly been used for both parts of this thesis. In a third part entitled findings, we will dig out from the previous sections the relevant knowledge and evidence regarding the link between HMS and NES; in particular, we will focus on the documented pathological mechanisms underlying such a connection and on the possible impact this could have on the management of the thoracic outlet syndrome. In conclusion, the research methods will be commented and trails for further scientific research will be proposed. Together with the findings, the conclusion should be considered as the most important sections of the thesis.

3. Joint hypermobility and the hypermobility syndrome

Double-jointedness, commonly apprehended by the unenlightened as no more than a peculiar bodily feature, is termed in the medical jargon as hypermobility or hyperlaxity. The condition, broadly speaking referring to the increased flexibility of joints, remained till late underrated by the rheumatological world for it is striking as an anomalous characteristic rather only in spectacular cases (as in contortionists). The recognition of less extreme forms of hypermobility for their deleterious effects on the musculoskeletal system (and therefore as a syndrome) occurred first in 1967 by Kirk, Ansell and Bywaters[8]. They introduced at the time the joint hypermobility syndrome (JHS) as the occurrence of *"musculoskeletal symptoms in otherwise normal subjects"*. Since then, the ailment has increasingly been described in medical literature and its definition and comprehension has steadily evolved and deepened. Quoting R. Grahame, a leading author in this field, joint hypermobility is currently apprehended as a "*commonly overlooked, underdiagnosed, multifaceted and multisystemic heritable disorder of connective tissues"*[9]. Thus, bearing in mind that the understanding of the condition remains only partial, we will attempt to realise an as exhaustive as possible description of the condition, specify its ins an outs pathologically speaking and try to outline the still remaining shortcomings of the latest researches.

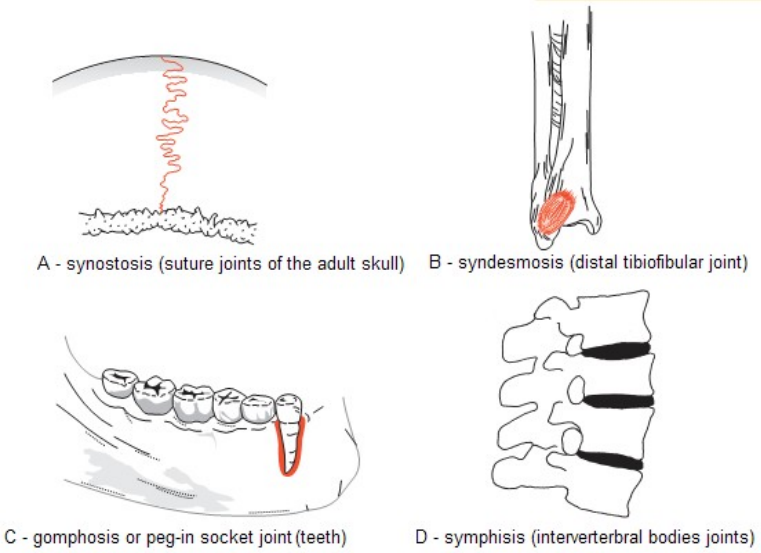
3.1. Introduction to the hypermobility: from the joints to their mobility and beyond…

One cannot expect to tackle the vast topic of hypermobility without setting about the just as vast theme of the articular system, for it is the one manifestly affected by hypermobility. Therefore, in this first section, we intend to provide the reader with concise and selected information about arthrology, to outline the facts relevant to our topic and to unveil a shade of the complex notion of hypermobility.

3.1.1. Basics of arthrology[10-12]

Joints, derived from the Latin "iunctus" (united, connected, associated)[13], are defined as sites of motion between adjacent bones, and which primarily functions are to

enable motion, bear the body's weight and provide stability. Although classifications slightly vary according to authors, we can distinguish three types of joints according to their structure but also according to the amount of motion they allow, as both depend on one another : the synarthrosis, the amphiarthrosis and the diarthrosis.



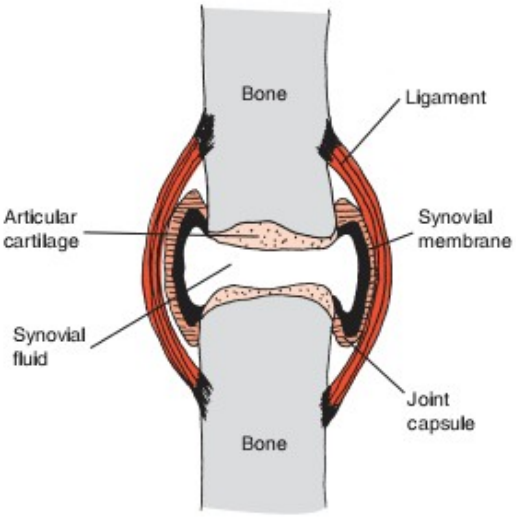
Picture 1 - Synarthroses (synostosis (A), syndesmosis (B), gomphosis (C)) and amphiartrosis (synchondrosis (not represented) and symphisis (D)), modified from *Clinical Kinesiology and Anatomy* by Lippert, 2011

Fibrous joints, also called synarthrosis permit very limited or no movement and comprehend several different subtypes. In addition to the natures and shapes of connecting bones which vary infinitely from one fibrous joint to another, it is rather the nature of their separation that supports their distinctions. We thus differentiate the synostoses (thin layer of fibrous periosteum), syndesmoses (ligaments and in-terosseous membranes) and gom-phosis (ligamentous).

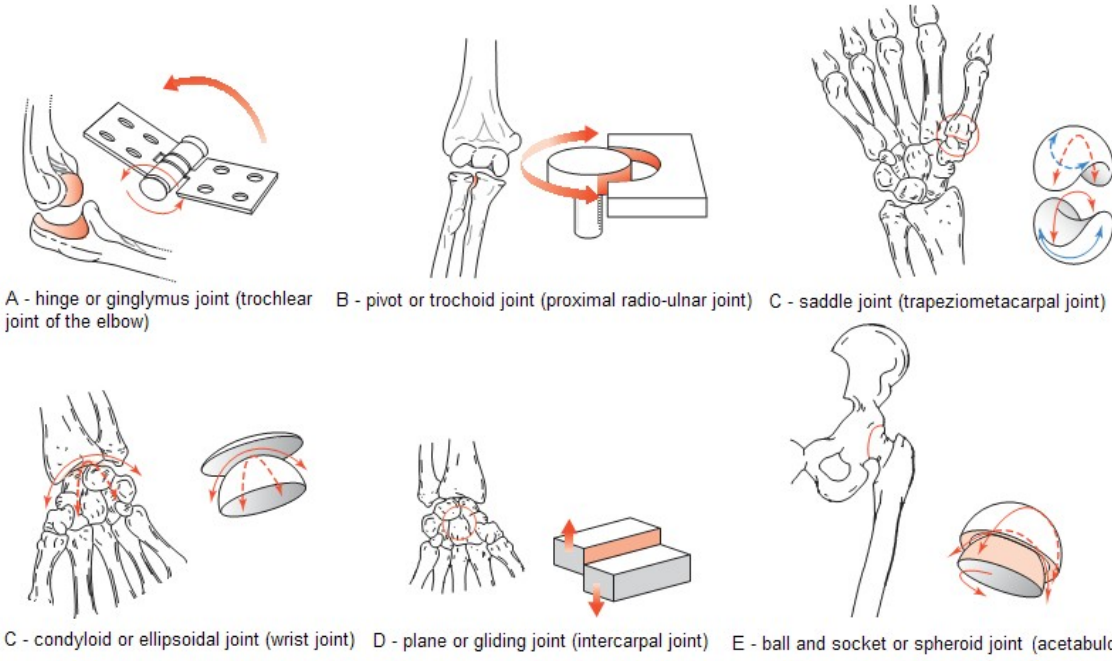
Cartilaginous or fibrocar-tilaginous joints, also called amphiarthrosis, permit relatively bigger motion than the purely fibrous types of joints (bending, twisting, compression…), yet are still characterized by the extensive stability they provide. We distinguish the cartilaginous synchondrosis (hyaline cartilage, as in the first sterno-costal articulation) and fibrocartilaginous symphysis (fibrocartilage).

Finally, synovial joints, also called diarthrosis, permit considerable movements and are subclassified into six subtypes according to their shape, axis and the type of movement that they allow (uniaxial, biaxial or multiaxial). We thus differentiate the hinge or ginglymus joints (uniaxial for flexion and extension), the pivot or trochoid joint (uniaxial for rotation), the saddle joints (biaxial for flexion, extension abduction, adduction and circumduction), the condyloid or ellipsoidal joints (biaxial for flexion, extension abduction, adduction and circumduction), the plane or gliding joints (uniaxial for simple gliding movements) and the ball and socket or spheroid joint (multiaxial for flexion, extension abduction, medial and lateral rotation, adduction and circumduction).

They are characterized by an external strong sleeve-like fibrous capsule holding the joint together. The joint capsule is then lined by a synovial membrane which secretes the lubricating, nourishing and filtering synovial fluid. Moreover, the bones' articular surfaces are covered with a smooth layer of articular cartilage (usually hyaline). Other structures possibly found in diarthrodial joints include menisci, labra (which deepen joint surfaces and improve the joints congruency and stability), discs or fat pads (which increase the protection of bony surfaces from compressive loads).



Picture 2 - schematic longitudinal cross section of a diarthrosis' joint capsule, from *Clinical Kinesiology and Anatomy* by Lippert, 2011



Picture 3 - Diarthrosis (ginglymus joint (A), trochoid joint (B), saddle joint (C), ellipsoidal joint (C), gliding joint (D), spheroid joint (E), from *Clinical Kinesiology and Anatomy* by Lippert, 2011

3.1.2. Joint stability and mobility, joint motion and joint movement[10,11,14-17]

As the joint characterizes a site of motion between two adjacent bones, it provides an intricate combination of stability and mobility, the former and the latter being function of one another. In other words, the more stabile a joint is, the less

mobility it can display, and conversely, a joint that allows a great deal of motion will provide very little stability. The extent to which a joint is stable (and therefore mobile) depends on three main factors : the articular surfaces, the ligaments and the muscles.

The shape, size and layout of the articular surfaces dictate to a large extent the kind and amount of motion available at a joint. Thus, adjacent articular surfaces that fit as puzzle pieces (so-called congruent) tend to restrain motion whereas rather dissimilar ones (incongruent) allow more mobility ; Besides, the curved or flat character of the articular surfaces plays a role in the type of motion (translation or rotation displayed by the articulation) and their degree of combination and the shape of the curved articular surfaces (which allows rather rotatory motion) plays a role in the axis along which can be provided the rotation. Finally, the less the “covering” of one articular surface by the other, the less stabile is the joint. Accordingly, any joint deformity, as in hip dysplasia for instance, would bear a non negligible effect on the joint’s stability and mobility.

The amount, nature and layout of ligaments, as well as, in the case of a synovial joint, the layout of the joint capsule, act as passive stabilizers by two mechanisms. On one hand, the visco-elastic properties of the fibrous tissue of the ligaments and of the external layer of the joint capsule allow a stability of the joint through its movements. On the other hand, it is the same fibrous tissue (meagrely vascularised contrary to the synovial internal layer of the joint capsule) that contributes to static position sense, sense, changing, direction of movement and regulation of muscle tone through the proprioceptors it contains, along with other tissue, notably muscular (see below).

The muscles whose tendons cross the joint act as active stabilizers by two mechanisms. As ligaments and joints capsules, muscle-tendon units are endowed with proprioceptors participating in the position and movement senses and muscle tone control. Besides, according to the Hilton’s law, muscles providing motion to a joint receive sensory inputs from the same sensory nerve as the joint itself and as the skin overlaying the insertion of these muscles. On the other hand, external forces applied to a joint are countered by the internal ones produced by the muscles and the ligaments. The muscle tone is in addition the major factor controlling stability in most joints. Accordingly, any condition in which the control of the muscle tone would be impaired, as in Down’s syndrome for instance, would affect the joint’s stability and mobility.

Ending	Principal location	Characteristics	Functional description	Information provided
Ruffini end organ	Superficial layers of the fibrous capsule	Low threshold, slowly adapted, encapsuled, myelinated	Direction and speed of movement, regulate muscle tone	Statistic position of the joint stretching of the tendon bundles
Pacinian corpuscule	Deep layers of the fibrous capsule, muscle fascia	Low threshold; rapidly adapted, encapsulated, myelinated	Acceleration and deceleration of the joint movement and pressure	Quick changes of joint movement
Golgi tendon organ	Ligaments near the joint	Low threshold, slowly adapted, encapsuled, myelinated	Direction of movement, record tension	Muscle contraction or stretching during contraction
Annulspiral ending of muscle spindles	Centers of intrafusal muscle fibers	Ecapsulated, thickly myelinated	Stretch receptor	Length change of the muscle
Flower-spray endings	At one or both sides of the annulospiral endings	Encapsulated, thinly myelinated	Stretch receptor	Length of the muscle
Cutaneous slowly adapting I	Merke'ls disc in dermis	Slowly adapted, small receptive fields, low threshold, unencapsulated	Spatial resolution, duration of skin indentation	Long-lasting mechanical stimulus on the surface of the skin
Cutaneous slowly adapting II	Ruffini corpuscules	Slowly adapted, large receptive fields, low threshold; unencapsulated	Stretching of the skin	Stretching of the skin
Cutaneous rapidly adapting	Meissner corpuscles	Rapidly adapted, small receptive fields, low threshold, encapsulated	Sense velocity	Slight movement of a hair
Cutaneous Pacinian	Pacinian corpuscules , subcutis	Very rapidly adapted, encapsulated	Acceleration or vibration	Discharges only when the velocity of skin deformation changes

Table 1 - Proprioceptors, simplified from *Innervation of the joint and role of neuropeptides* by Konttinen YT, Tiainen VM, Gomez-Barrena E et al, 2006[16]

As a result of their inherent stability and mobility, joints are in addition characterized by the motion they allow. From an arthrokinematics point of view, motion at the joint is described only two-dimensionally as either rotatory or translatory (namely linear). Again, it is the joint's features which determine the available type of motion: while most cartilaginous and fibrous joints allow linear movement, syovial joints allow both rotation and translation. From an osteokinematics standpoint on the other hand, joint's motion occurs three-dimensionally, along three axis and in three planes (sagittal, frontal and transversal) perpendicular to one another.

The motion available at a specific joint, termed as the joint's range of motion (ROM), is measured along these same coordinates and expressed in degrees according to the plane in which the movement occurs and the direction of the movement: flexion and extension for the sagittal plane, abduction and adduction for the frontal plane, lateral rotation, medial rotation, pronation and supination for the transversal plane. Additionally, a joint's ROM can be determined either actively (movement performed by the patient himself under the instruction of the examiner) or passively (movement performed by the examiner), the latter being usually greater than the former ; thus,

whilst the passive ROM roughly renders the soundness of the joint's structure, the active ROM reflects in addition the integrity of the muscular and nervous system responsible for its movement. Thus it appears that more than the fibrous, cartilaginous or synovial structure of a joint, it is also the movements and their amplitudes available at a joint that characterize it and norms have been determined accordingly. However, the validity of these normative data is disputed, numerous studies having shown that in spite of the absence of pathological process, ROMs decrease with age, are greater in females and some ethnicities and varies according to specific environmental factors. Lastly, it is interesting to note that the ROM at a given joint is observed as following physiologically a Gaussian distribution in the population

3.1.3. Joint hypermobility and its various, almost identical, related conditions

Getting to the heart of the matter, one can find oneself bemused by the various denominations of the hypermobility, for each of them bear divergent, subtle or no differences in author's minds: flexibility, hyperlaxity, joint instability, hypermobility but also HMS, JHS, BJHS, Ehlers-Danlos syndrome hypermobility type (EDS-HT), are some amongst the various appellations interchangeably used when addressing our topic. Better than arbitrarily judging one denomination as being the only valid and worthy one, we rather intend to provide the reader with a bit of terminologistic rigour.

If flexibility, hyperlaxity and joint instability are undeniably related to joint hypermobility, the use of one instead another however results from a too simplistic conception. Indeed, an informal way of addressing someone presenting hypermobile joints is to say he/she is very flexible. And the confusion may originate in this popular saying because, as it is often the case, the most common words can prove to be the most difficult ones to define scientifically. In his book, *Science of flexibility*[17], Alter reviews the many meanings of the word flexibility through the various researches it was the primary topic of. It appears that the flexibility is unequivocally linked to the ability of displaying movement but can refer either to one or several joints. If some authors have a rather circumspect approach of the notion of movement (strictly referring to its range), others choose to extensively precise its quality (fluidity, speed, pain-free character). In other words, they choose to add a normative character to the movement and hereby to

the flexibility. In contrast, the term hyperlaxity, when pertaining to a joint, genuinely conveys a sense of abnormality for it refers to a state of increased looseness (the latter being primary the fact of ligaments in the case of joints)[18]. According to Alter, laxity is even related to the notion of stability, and joint hyperlaxity would therefore refer to joint instability. Nevertheless, to add to the confusion and probably out of reluctance to gallicize an English term, joint hypermobility is rather translated by "hyperlaxité articulaire" (literally articular hyperlaxity) in French publications[19]. But joint hypermobility on one hand, and joint hyperlaxity and joint instability on the other hand do constitute distinct entities. In an attempt to better differentiate the two conditions, Alter focuses on the arthrokinematics. He characterizes the loss of joint stability by an increased or normal ROM, an increased proportion or aberrant translation movements and aberrant coupled movements and states that the hypermobility is associated with an increased ROM, normal ratio of transitional movement and normal coupled movements. Joint instability and joint hypermobility, although distinct from one another, nevertheless remain fundamentally correlated as, as it has been shown by Cameron et al. (2010)[20], joint hypermobility, at least in the glenohumeral joint, can lead to glenohumeral joint instability. For the purpose of this review, we will therefore consider joint flexibility as referring to a normal ROM, joint hypermobility as an increased ROM in the absence of pathology of the joint, and joint hyperlaxity and joint instability as a pathological state of the joint, unless otherwise specified.

Alongside, as a result of a still currently evolving nosology of the condition[21], there are many naming of syndromes after the common feature of hypermobility. If some of them are almost archaic (the term BJHS was modified from the JHS naming introduced by Kirk, et al. in 1967[8]), the newer denomination of EDS-HT is more in accordance with the current status of the scientific researches, especially in the field of genetics[22-24]. It has to be noticed that it is rather the topic of the publication that will decide after the naming of the condition. If physiotherapists and rheumatologists choose to talk about BJHS, JHS or HMS[1], thus highlighting its symptomatic character, geneticians emphasize the fact that joint hypermobility constitutes a heritable disorder of connective tissues[7] and will therefore rather speak of EDS-HT[7,22,23]. The denominations BJHS, JHS and HMS (for the most common) do appear very similar but still convey a different, yet very subtle understanding of the condition. Indeed, the appellation BJHS (given in the absence of evidence of life expectancy threat) renders an

erroneous belief of benignity, concealing its mutlisystemic and highly deleterious character. Likewise, the denomination JHS restricts the symptomatic expression of the disorder to the articular system while the range of extraarticular manifestations is varied[2]. The denomination HMS appears thus more objective and is therefore favoured by some authors. Similarly, a common mistake is to confuse joint hypermobility and HMS (or one of its other denominations). If hypermobility constitutes a multifactorial feature pertaining to the joints (which show a beyond-the-norm mobility), the HMS defines a pathological condition, subjected to diagnosis and classification, and resulting from the former[18]. According to Toft et al., HMS can be defined as the occurrence of secondary consequences of their generalized joint hypermobility, such as pain or joint dislocation, independent from the underlying diagnosis[25]. The latest denomination of the condition, EDS-HT, emerged in 1997 after the Villefranche conference which aimed at better classifying the Ehlers-Danlos syndromes (EDS)[26], themselves categorized amongst the HDCTs. Since then, HMS and EDS-HT have been progressively been recognized as a the same entity, yet potentially different in the presentation of the symptoms, but forming a continuum of phenotypes, which is related to activity and age rather than to the underlying genetic defect[21].

Having said so, the complexity of our topic appears perhaps even more startling and accordingly, it seems unattainable to judge one denomination over the other without showing subjectivity or worse, inaccurateness. Nevertheless, as this review is addressed under the angle of physiotherapy, we will go along with choices made by peers before and prefer the denominations of joint hypermobility and HMS as defined respectively by Grahame and R. Keer. Through this thesis, the joint hypermobility will be defined as a greater ROM than the norm (gender, age and ethnic origin taken into account), linked to an increased looseness of joint, genetically caused by an aberration in the encoding of molecules of connective tissues in otherwise normal individuals[18]; it constitutes the hallmark of HDCTs. The HMS will refer to an HDCT as the pathological condition stemming from joint hypermobility, present in otherwise normal children or adults and characterized by both musculoskeletal and extraarticular symptoms[1].

3.2. Assessment of hypermobility and diagnosis of hypermobility syndrome: historical and nosologic perspective on the available diagnostic tools.

In order to understand how hypermobility is assessed and how its pathological expression, the HMS, is diagnosed, it is necessary to adopt a broader perspective. Indeed, if an increased laxity of joints _whether it is generalized or not_ can be noticed in a variety of conditions, it is definitely more conspicuously seen in the HDCTs, a still relatively nebulous collection of genetic diseases. Thus, over the next few paragraphs, we will tackle the last century's scientific developments which came in for the HDCTs; in parallel we will present the evolution of their classification on one side and diagnosis on the other, as the latter required the creation of reliable and valid tests. Finally we will discuss the differential diagnosis of JHS with the other HDCTs notably.

3.2.1. An insight of the history of the hereditary disorders of the connective tissue

The first mention of hypermobility is attributed to Hippocrates at about -400 BC. The ancient Greek physician described the Scythians, some Iranian horse-riding nomads, inhabiting the region which is now known as Ukraine, as presenting humidity, flabbiness and atony, such as they were unable to use their weapons. In its clinical description, he underlined the disability it represented especially in warfare, as, due to the hyperlaxity of their shoulders and elbow joints, the Scythians were prevented from drawing their bows efficiently. Then again, until the 19th century, the condition remained relatively dismissed up till being noticed as an important feature of other syndromes such as the Marfan syndrome (MFS) and the Ehlers-Danlos syndrome (EDS)[27],which belong to a vast group of inherited diseases, the HDCTs. The HDCTs can be defined as *"a group of phenotypically related inherited conditions caused by aberrations in genes encoding [the proteins of] the connective tissue matrix (collagen, elastins, fibrillins and tenascins)"*[28]. They comprehend, for the most famous rheumatological ones _that is primarily pertaining to the locomotor system_ the MFS, the EDS and the ostogenesis imperfecta (OI)[28,29]. The JHS rather being considered

nowadays as a “forme frustre” (ie attenuated) of a genetic connective tissue disease[22], they thus compose, as one could say, its most malevolent but rarer kin.

The first clinical description of the EDS in medical literature was done by a Russian dermatologist named Tschernogubow in 1892[30]. But the syndrome received its definitive name and hence scientific respectability in 1936 after the name of two dermatologists, respectively Danish and French who separately described the condition in 1901 and 1908[31]. Concurrently, in 1896, a French paediatrician named Antoine-Bernard Marfan described the case of a 5 years old girl with long slender digits, long bone overgrowth and muscle hypoplasia, which he first named dolichosténomélie and that would later become the Marfan syndrome. It is interesting to note that he in fact at the time described what is now know as the Beal syndrome, or congenital contractural arachnodactyly, a rarer form of HDCT, characterized in 1972[31,32]. As for the osteogenesis imperfecta, after centuries of miscellaneous descriptions under varied appellations, and of confusion with other post natal acquired diseases such as rickets or osteomalacia, the disease received its current name shortly before 1850 after the observations of a Dutch anatomist, Willem Vrolik, realized on a newborn infant with numerous fractures and hydrocephalus[33]. Moreover, and in parallel with the recognition of joint hypermobility as a distinctive hallmark of the above mentioned diseases[22] , the feature was progressively associated over the last 50 years to a variety of orthopaedic and rheumatological symptoms, in the absence of obvious widespread connective tissue abnormality[27]. Rheumatological symptoms, notably effusion and pains in a group of patients with increased joint laxity led notably Kirk et al. to define the hypermobility syndrome in 1967[8]. With the increasing report of cases, sometimes showing baffling overlapping features or, to the contrary, unexpected differences, and along with the intensifying evidence of the connective tissue’s pervasive involvement, it soon became evident that an attempt of classification was to be made[29,31,34].

The first attempt of classifying the HDCTs occurred in 1986 at Berlin and resulted in the Berlin nosology for HDCTs published in 1988, which notably delineated 10 subtypes of EDS[35]. Pursuant to the partial elucidation of the underlying genetic and biomolecular mechanisms of the HDCTs[36], the nosology of EDS was revised in 1997 at Villefranche-sur-mer[26]. The 1997 Villefranche nosology recognizes six subtypes of the EDS based on clinical characteristics, mode of inheritance and biochemical and molecular findings ; for each subtypes, major and minor clinical diagnostic criteria were

defined (see table 2 for diagnostic criteria of EDS-HT). Besides, the elucidation of the molecular basis of the MFS in 1991, identifying FBN1 mutations as the underlying cause of the disease, led to a correction of to 1986 Berlin nosology for the MFS in 1996 with the 1996 revised Ghent nosology. The latter acknowledged the contribution of molecular diagnosis and defined major and minor criteria in the skeletal, ocular, cardiovascular, dural, integumentary and pulmonary systems for the MFS[37].

1997 VILLEFRANCHE DIAGNOSTIC CRITERIA FOR THE EDS-HT (FORMERLY KNOWN AS EDS TYPE III)
Major criteria :
1. Skin involvement (hyperextensibility and/or smooth, velvety skin) 2. Generalized joint hypermobility
Minor criteria :
1. Recurring joint dislocations 2. Chronic joint/limb pain 3. Positive family history
Special comments :
1. Skin extensibility is variable. The presence of atrophic scars in individuals with joint hypermobility suggests the diagnosis is classical type 2. Joint hypermobility is the dominant clinical manifestation. Certain joints such as the shoulder, patella, and temporomandibular joints dislocate frequnelty 3. In rheumatologic practice, large numbers of patients present with generalized joint hypermobility. It is important to distinguish these individuals froms those affected with the hypermobility type of EDS. There is considerable debate as to the causal interrelationships, if any between the phenotypes in such persons and in those with the hypermobility type of EDS 4. Musculoskeletal pain is early in onset, chronic, and possibly debilitating. The anatomical distribution is wide and tender points can sometimes be elicited. A tender point is defined as an area that, when palpated with the thumb or 2 or 3 fingers, will be painful at pressure of 4kg or less. 5. For management see Steinman et al [1993]*
* reffers to STEINMANN, B., ROYCE, PM., SUPERTI-FURGA, A. The Ehlers-Danlso syndrome. In ROYCE, PM., STEINMANN, B. *Connective tissue and its heritable disorders : molecular genetic and medical aspects*. 1st Ed. pp 351-407. New-York: Wiley-Liss.

Table 2 - 1997 Villefranche diagnostic criteria for the EDS-HT, reproduced from *the Ehlers-Danlos syndromes : revised nosology, Villefranche, 1997*, by Beighton, De paepae, Steinmann et al., 1998

If, as established above, joint hypermobility assuredly constitutes a distinctive hallmark (yet more or less patent) to all the HDCTs[22], then for this very same reason, its apprehension is undeniably related to theirs. Indeed, as scientific advances unveiled the tissular, biomolecular and genetic inner-workings of these diseases, the understanding of their common denominator, the joint hypermobility, became more accurate. Delineating a group of connective tissue diseases, underlying their inherited character, attempting to classify them and accordingly to better recognize them, represents the last century's and most likely the next one's scientific challenge in the domain of the HDCTs[21]. Indeed, notably for EDS, the classification demonstrates undeniable shortcomings as many patient present overlapping forms which cannot be classified

satisfactorily into one of the six recognized categories. Moreover, while some authors genuinely consider the HMS and the EDS-HT (formerly known as type III) as the same entity[38], others, more prudently consider them as *"indistinguishable"* from one another[28], yet still argue about their debatable association[29,39,40] or even consider them as two distinct clinical entitites[41]. The most consensual approach might be the one of Tinkle et al[21], who, in their 2009 publication reckon that, given the actual impossibility to distinguish EDS type III and HMS, but the feasibility of their differentiation from other HDCTs, the union of the two diagnostic labels serves better the clinical population suffering from them. Thus, none would argue that a reappraisal of the relationship between EDS and HMS and of their classification is suitable, but also doomed to follow the pace of the medical discoveries, notably in the domain of genetics[42,21].

3.2.2. Diagnostic tools used for detecting hypermobility and diagnosing the hypermobility syndrome: Beighton score and Brighton criteria

As mentioned above, as Scientifics were attempting to classify the HDCTs, they needed to develop reliable and reproducible scoring tests for their distinctive hallmark: the increased joint laxity. The latter being considered (by the way mistakenly) as representing the upper extreme in a Gaussian distribution[22] of the joint mobility, the establishment of scoring systems for hypermobility was also related to the general trend of establishing ROM norms[27].

3.2.2.1. From the Carter and Wilkinson score to the Beighton score

The first scoring system for generalized joint hypermobility was introduced by Carter and Wilkinson in 1964 within the framework of one of its* possible issues: the congenital dislocations of the hip. It was then modified by successive authors at the whim of the pathological studies and scientific publications. It is the modification of the Carter and Wilkinson's scale by Beighton et al. in 1973 called the Beighton score[43] and presenting a set of 9 tests of single or composite joint movement to each of which is

* now known to be varied

affiliated one point (see table 3), that eventually gained general acceptance[27]. Indeed, the accuracy of the test relies in the chosen examined joints and their representativeness in terms of global mobility. In their reference book, "hypermobility of joints", Beighton et al. develops this assertion and give three main reasons why the Beighton scale was then preferred over other scoring systems for generalized joint hypermobility[44]:

- scoring systems using hyperextension of the middle rather than the little finger exclude too many persons
- scoring systems using ankle movements, although perhaps appropriate for dancers, are unlikely to show much variations between individuals in normal populations
- scoring systems including trunk and hip movements (composite joint movement) are more likely to reflect generalised articular laxity.

Although other sophisticated mechanical devices affording a greater precision exist, the Beighton scale for generalized hypermobility presents the advantage of its simplicity, fastness and easiness of reproducibility; it allows large population studies, facilitates epidemiological work and is therefore still mostly used[44]. Even when compared to other scoring systems of generalized hypermobility, notably the Rotès-Querol scale (more popular in France), or the Hospital del Mar score (rather used in Spain but at first aiming at defining the HMS and not scoring the joint hypermobilty), the Beighton scale proves its reproducibility and validity[45,46].

THE NINE POINT BEIGHTON HYPERMOBILITY SCORE			
Illustration	Ability to :	right	left
	1. passively dorsiflex the fifth metacarpophalangeal joint to ≥ 90°	1	1
	2. oppose the thumb to the volar aspect of the ipsilateral foream	1	1
	3. Hyperextend the elbow to ≥ 10°	1	1
	4. hyperextend the knee to ≥ 10°	1	1
	5. place hands flat on the floor without bending the knees		1
One point may be gained for each side for manoeuvres 1 to 4 so that the hypermobility score will have a maximum of nine points if all are positive.			

Table 3 - The nine point Beighton hypermobility score (with illustration of the test's items) modified from *hypermobility of joints*, by Beighton, Grahame and Bird, 2012.

Nevertheless, as it will be shown in the following section of this thesis, joint laxicity is generally more important in children and adolescents and decreases with age; females are on the other hand more mobile than males at any age and the prevalence of hypermobility changes according to races[47,48,49]. Furthermore, as Grahame reminds us in one of his numerous warning publication about hypermobility[2], it has been established that hypermobility is more often pauciarticular than poly articular and that it does not have to be generalized to produce symptoms[48]. It thus brings the problem of the cutoff score (conventionally but rather arbitrarily at 4/9) which is chosen in the Beighton scale to diagnose generalized joint hypermobility and consequently to diagnose HMS and no agreement seem to have yet been found[47,50,51].

3.2.2.2. Towards a better recognition of the connective tissues' involvement in the hypermobility syndrome: the Brighton criteria

Scientifics also needed to be able to distinguish HDCTs from one another and with this aim in mind, developed standardized clinical evaluations and tests but also laboratory methods of diagnosis. As the point of this thesis truly is the joint hypermobility (rather than HDCTs in general) we will not develop the laboratory methods of diagnosis here as up to date, none have been found for the HMS[31,51].

The most accurate way of diagnosing HMS nowadays, in the absence of available laboratory tests, seems to be the Brighton criteria proposed in 1999* and published the following year (see table 3 above)[52]. It was proposed in order to amortize the above mentioned shortcomings of the Beighton scale and in order to tally with the expanding understanding (notably biomolecular) gathered about HMS. Indeed, in the light of the scientific advances and because of the acknowledgment of the deficient collagen's ubiquitous character, the involvement of other body systems than the musculoskeletal one became evident. Thus emphasising the suspected autosomal dominant inheritance pattern of the HMS, and the importance of the patient's anamnesis, the Brighton criteria also presents the advantage to comprise two sections:

* conventionally determined for the BJHS out of familiarity with the syndrome's denomination, but as observed earlier in this review and by the authors themselves, HMS or JHS would be a more appropriate denomination.

- the major criteria are focused on the musculoskeletal system : with the Beighton score (to which a cut-off score of 4/9 has been attributed for being positive) and
- the minor criteria are focused on the possible affliction of other body systems, in which the deficient collagen might be expressed

THE REVISED DIAGNOSTIC CRITERIA FOR THE BJHS
Major criteria :
1. A Beighton score of 4/9 or greater (either currently or historically) 2. Arthralgia for longer than 3 months in four or more joints
Minor criteria :
1. A Beighton score of 1, 2 or 3/9 (0, 1, 2 or 3 if aged 50 +) 2. Arthralgia (≥ 3 months) in 1-3 joints, or back pain (≥ 3 months), spondylosis, spondylolysis/spondylolisthesis 3. Dislocation/subluxation in more than one joint, or in one joint on more than one occasion 4. Soft tissue rheumatism ≥ 3 lesions (e.g. epicondylitis, tenosynovitis, bursitis) 5. Marfanoid habitus*: tall, slim, arm span > height; upper segment:lower segment ratio less than 0,89, arachnodactily) 6. Skin striae, hyperextensibility, thin skin or abnormal scarring 7. Eye signs : drooping eyelids or myopia or antimongoloid slant 8. Varicose veins or hernia or uterine/rectal prolapse
The BJHS is diagnosed in the presence two major criteria or one major and two minor criteria or four minor criteria. Two minor criteria will suffice where there is an unequivocally affected first degree relative. BJHS is excluded by the presence of Marfan or Ehlers-Danlos syndromes (other than the EDS hypermobility type, formerly EDS III) as defined by the Ghent (1996) and Villefranche (1998) criteria respectively

Table 4 - The revised diagnostic criteria for the BJHS, reproduced from *The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS)*, by Grahame, Bird, and Child, 2000.

Nevertheless, and despite the lesser risk to overlook HMS than with the sole use of the Beighton scale[53] the Brighton criteria still appears less used than the Beighton score[39,54]. Yet, an unexpected result to the increasing usage of the Brigthon criteria in medical studies was the suggestion along which many cases of HMS were overlooked[39]. In an attempt to increase the awareness of the medical institution to the (suspected) widespread character of HMS in the population, Hakim and Grahame proposed in 2003 a simple five part self-report questionnaire (see table 6). It represents a possible adjunct to the assessment of the origin of musculoskeletal problems[55].

As exposed above, the Beighton scale, Brighton criteria and questionnaire by Hakim and Grahame are the consecrated and specific diagnostic tools to assess hypermobility and HMS. They nevertheless possess more or less shortcomings, pursuant to the very feature sof HMS (notably its distribution amongst population). On the other hand, if the sole performance of these tests serves to the diagnosis of the

* see table 5

condition, others have to be performed within the framework of its therapeutic management (pain scoring, ROMs…)[56]. For more precisions, we send the reader to the section 5: "clinical relevance in physiotherapy".

THE MARFANOID HABITUS
1. high arched palate 2. arachnodactyly : which can be demonstrated by a positive wrist sign according to Walker (ability ot wrap the thumb and fourth finger of one hand around the opposite wrist such as the nail bed of the digits overlap with each other) or by a positive thumb sign according to Steinberg (projection of the thumb which is held across the palm of the same hand well beyond the ulnar aspect of the hand) 3. pectus excavatum or carinatum 4. scoliosis : a scoliosis higher than 20% is a major criteria in MFS and present in 60% of cases; it is also a cardinal sign in the EDS kyphoscoliotic type and may also present to a milder degree in JHs, other variants of EDS and OI type I 5. arm span/height ration greater than 1,03 6. tall stature with lower limb length (floor to pubis)/upper body (pubis to crown) ratio greater than 0,89 7. foot length (heel to first toe)/height ratio greater than 0,15 8. hand length (wrist crease to third finger)/height ratio greater than 0,11.
The marfanoid habitus defines a well recognized phenotype in MFS with possible mild variants that do not express the complete MFS (habitus found in the absence of ocular or cardiac involvements, typical for the MFS). It can be found up to 1/3 of the JHS cases.

Table 5 - The Marfanoid habitus, reproduced from *Joint hypermobility and skin elasticity: the hereditary disorders of connective tissue*, by Hakim and Sahota, 2006

FIVE PART QUESTIONNAIRE FOR BJHS
1. Can you now (or could you ever) place your hands flat on the floor without beinding your knees ? 2. Can you now (or could you ever) bend your thumb to touch your forearm ? 3. As a child, did you amuse your friends by contorting your body into strange shapes OR could you do the splits ? 4. as a child or teenager, did your shoulder or kneecap dislocate on more than one occasion ? 5. Do you consider yourself double-jointed ?
Answer in the affirmative to two or more questions suggests hypermobility with sensitivity 80-85% and specificity 80-90%

Table 6 - Five part questionnaire for BJHS, reproduced from *A simple questionnaire to detect hypermobility : an adjunct to the assessment of patients with diffuse musculoskeletal pain*, by Hakim and Grahame, 2003

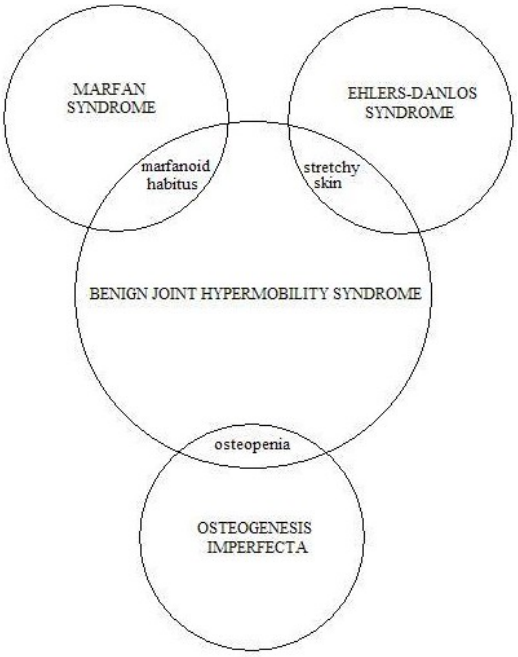
3.2.3. Ensuing differential diagnosis for the hypermobility syndrome

Because of their overlapping features[19,29,31], the differential diagnosis of the HMS is classically done with the other main types and subtypes of HDCTs : MFS, OI and EDS. Indeed, although each disorder presents itself with distinct phenotypes (at least on paper) and can be characterized by cardinal features, the clinical experience proves that, in theses diseases, they can resemble one another, only to vary in degree[29]. The Venn diagram, which illustrates the overlap features between the four major

HDCTs and show that HMS maintains a central position sharing key features with MFS, OI and EDS is reproduced in the picture 4.

A large number of authors[3,29,31,51,57] agree on the necessity of correctly diagnosing HMS when a HDCT is first suspected; they identify, according to the topics of the publications, two main reasons for doing so :

- firstly in order to rule out, as we called them earlier, its rarer but more malevolent kin; if HMS presents a great deal of comorbidities, it nevertheless remains a *"non-life-threatening forme frustre of an HDCT"*[29] with a normal life expectancy (hence, the denomination of benign often used). OI, MFS and EDS on the other hand do have potentially life-threatening complications. Amongst other, we can quote: aortic dissection for MFS, arterial and gastrointestinal rupture for EDS, respiratory and neurological complications for OI…

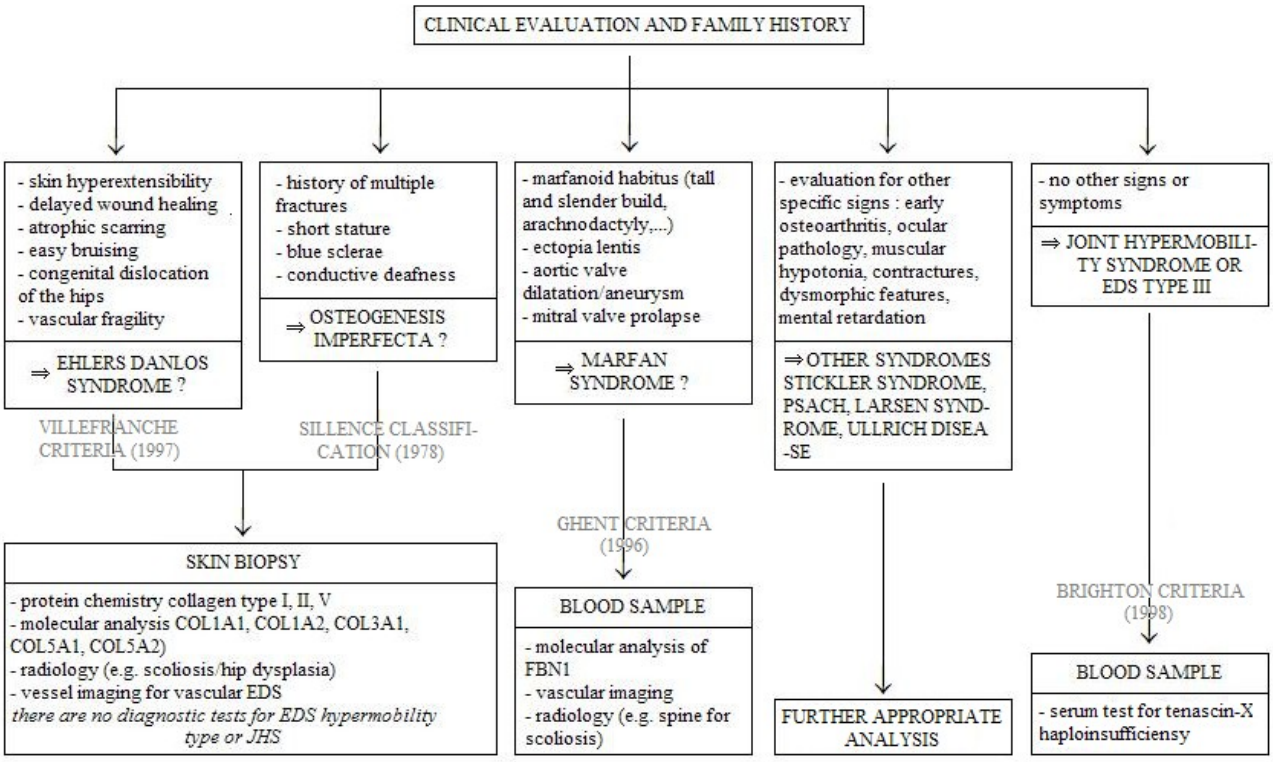


Picture 4 - Venn Diagram, reproduced from *Joint hypermobility* by Hakim and Grahame, 2003

- secondarily in order to provide the best management of its condition to the patient: the erroneous diagnosis of another (more serious) rheumatic disease would give rise to an inappropriate management; on the other hand, the negation of the patient's pathological status (which still can occur because of the HMS underrecognition) actuate the patient's dissatisfaction and distrust towards the medical profession and delays the relief of its symptoms[29].

The diagnosis of any HDCT should rely on three main items which are : the patient's clinical evaluation, (aiming at detecting any HDCTs' characteristic symptoms), the checking of the family history (aiming at outlining inheritance modes) and if available, the performance of laboratory tests under the form of blood sample or skin biopsy (aiming at detecting genetic defect)[51]. Each different HDCTs' possible range of symptoms is defined according to its diagnostic criteria (Villefranche criteria for EDS, Sillence criteria for OI, Ghent criteria for MFS and Brighton criteria for

HMS). The examiner therefore is entitled to rely on these and the performance of further appropriate analysis to settle a diagnosis. Probably the simplest way to summarize the steps of performing the differential diagnosis of HMS, is the diagram proposed in 2006 by Malfait et al[7]. and slightly modified by Hakim and Sahota the same year[57]. The diagram describes the possible findings of the clinical examination, the possible diagnosis and their confirmation by laboratory tests. A synthetic version of both tables is presented in picture 5.



Picture 5 - Steps for performing the differential diagnosis of JHS modified from *Joint hypermobility and skin elasticity: the hereditary disorders of connective tissue* by Hakim AJ and Sahota A, 2006 and *The genetic basis of the joint hypermobility syndromes* by Malfait et al, 2006.

Nevertheless, and contrarily to what is suggested by Malfait et al.'s diagram, the performance of laboratory tests for the diagnosis of HMS remains extremely rare. Indeed, as it is pointed out in the same publication, haploinsufficiency of tenascin-X can account only for a small subset of patients with joint hypermobility (5-10% of EDS type III/HMS). Thus, better for the reader to assume that, up to that date, there are no available confirmatory battery of laboratory tests for HMS. This assumption is clearly done by Tinkle et al in their 2009 publication[21], in which they even take the extra step by stating that patients are labelled as BJHS/HMS/JHS/EDS type III sufferers when no other disorder could be elicited, thus making the HMS a *per exclusionem* or default

diagnosis and outlining, if need is, the scarcity of diagnostic tools for this condition and their shortcomings. Another 2001 study by Grahame and Bird about British Rheumatologists' perception about HMS argue of the same fact but for slightly different reasons : observing that 61% of their respondents require a negative laboratory screen before making a diagnosis of HMS, they argue that the HMS is diagnosed rather by exclusion than inclusion and that this could denote a lack of confidence in one's clinical findings[54].

Note: We draw the reader's attention to the fact that the above mentioned differential diagnosis are given for an adult population, which is the target of this review of literature. For children the case is slightly different, as there is the possibility to perform differential diagnosis with other conditions (as HMS can give rise to other symptoms than in adults) such as juvenile arthritis for instance[58].

3.3. Epidemiology: prevalence and distribution amongst the population of the joint hypermobility and hypermobility syndrome

When introducing JH and/or HMS, many generalist publications (and other more targeted ones) endeavour to provide their readers with actual figures regarding its prevalence. Nevertheless, the profusion of diverging numbers (claimed according to the different sources retrieved by the authors) generates a manifest feeling of confusion. Trough this section, we will attempt to clarify the actual knowledge about the prevalence distribution of JH and HMS in the population.

3.3.1. About the difficulty to interpret epidemiologic studies

First of all and as remind us Hakim and Grahame in a 2003 publication, *"it is important to distinguish hypermobility, which describes the often asymptomatic increased range of joint or spinal movement, from hypermobility syndrome, its symptomatic counterpart"*[51]. This unarguable distinction _already established at the beginning of this review_ takes on its full meaning when attempting to characterise the epidemiology of JH and HMS. Indeed, most hypermobility-targeted studies base the

integration of subjects on the use of the Beighton scale (with often arbitrarily-set cut-off scores)[47,50,51].

Yet, and as it has been shown earlier in this work, the method presents several shortcomings, notably for it lacks to take into account the physiological variations of ROM amongst individuals. Most importantly, the method solely reckons the generalized joint hypermobility*, and not its pathological expression, the HMS. In this last point resides the necessity to distinguish JH and HMS. And thus, if it is nowadays possible to have a rough idea of the generalized joint hypermobility distribution amongst populations, its estimation for HMS still remains uncertain.

Sharing this feeling of confusion, Simmonds and Keer, in a 2007 publication[59], mention another crucial point weighing in the definition of both conditions' epidemiology: the screening of the population. If some authors purposefully use certain profiles, other conduct studies on the populations which are "at their disposal". This necessarily brings about several bias which must be taken into account in the calculation of prevalences: one must ask oneself if the study concerns a general population or a clinical (rheumatological for most) one ? Or again, which is the targeted group (schoolchildren ? preadolescents ? pregnant women ? militaries ? New Zealanders ? Egyptians ?....) ? And how is it possible to categorize them ?

Despite the very large amount of hypermobility-targeted studies on populations, the prevalence of JH (and henceforth HMS) remains unclear. It seems that the establishment of definite prevalences suffers from the shortcomings of the assessment methods for JH and HMS. And as we already mentioned, they are themselves bound to the scientific advances regarding the definition of both conditions.

3.3.2. A difficultly countable distribution of the generalized joint hypermobility which yet is known to vary with age, gender, ethnicity and occupation

In a rather recent literature review (2007), Remvig, Jensen and Ward examined the epidemiology of the general joint hypermobility. They also confronted the frequency of some associated disorder found in hypermobile subjects with the actual criteria used

* putting aside milder forms of hypermobility, the condition being rather pauciarticular than polyarticular[48]

for the diagnosis of HMS (Brighton scale)[47]. Their review presents the major interest to be the only one up to that date* focussing on the distribution of hypermobility and HMS. Gathering studies using Carter and Wilkinson criteria and Beighton scale as assessment tools and using as various cohort studies as schoolchildren, musicians, militaries,… their review support the variability of JH prevalence amongst different populations. However, as Castori observes in a 2012 generalist publication about EDS-HT[3], Remvig et al.'s review is not systematic, the alleged figures are thus to manipulate with caution and therefore we will not put forward any.

Nonetheless, Remvig et al. (as other argued before them) evidence four criteria of variability for generalized hypermobility:

- **the age:** generalized hypermobility is more prevalent in children than in adult population; moreover, numbers of positive hypermobility tests is age and sex-related, namely, generalized hypermobility steadily decreases with age, and is more important in girls than in boys. An interesting example is the 2004 publication by Hakim, Cherkas, Grahame et al.. Studying the genetic epidemiology of hypermobility on a population of female twins in the UK, they demonstrated that *"the prevalence of hypermobile joint declined with age, falling from 34% in subjects ages 20-30 years to 18,4% in those ages 60 years or older"* [23].

- **the gender:** women are more affected by hypermobility than men, compiled data showing a steadily higher number of women affected in the studies. It has to be noticed that in their 2003 publication Hakim and Grahame state that hypermobility is about 3 times more common in females than males[51]. In a 2006 publication however, Hakim and Sahota[57] estimate that *"generalized or polyarticular hypermobility may be present in 10 to 30% of men and 20 to 40% of women in adolescence and young-adulthood"*.

- **the ethnicity:** indubitable before, and confirmed here, is the strong disparities regarding the distribution of joint hypermobility amongst different races. Asians appear to be the most likely to be affected by hypermobility, followed by Africans and finally with the lowest estimated prevalence, Caucasians.

- **the occupation:** quite often forgotten by publications, but put forward here, the prevalence of hypermobility is found to be also related to the subjects' occupation. More particularly, two populations on which have been conducted epidemiologic studies are mentioned : ballet dancers and musicians. For the ballet dancers, Remvig et

* to our knowledge, despite an extensive research

al. specify that hypermobility was also presents in the joints which are not exposed to stretching exercise (outlining the hereditary rather than acquired character of hypermobility). In musicians similarly, the prevalence is found to be higher[60]. Those findings bring about the eventuality a positive facet to hypermobility. In their 2003 earlier publication, using those same occupation-targeted studies as Remvig et al.[61,62], Hakim and Grahame argue that hypermobility could act for these populations as a positive selection factor (for entry into the ballet corps but also for sparing pain to hypermobile musicians in comparison with their less flexible peers). Nevertheless, this assertion is questioned by other authors having found that ballet dancers displaying GJH present more vulnerability to musculoskeletal and psychological afflictions, and lower physical fitness despite equivalent training than their non-hypermobile peers[63]. On the other hand, according to them, the prevalence of hypermobility in athletes questions its advantageous character as the rate of soft tissues injuries seems also to be higher. This has been demonstrated notably in a 2012 cohort study of professional soccer players in England which found more missed days for training and match play in hypermobile subjects[64].

Echoing the introduction of this section, Remvig et al. also outline the difficulty to assess JH prevalence and recommend *"several systematic tasks"* to be performed: *"[the definition] of normal joint range of motion sorted according to age, sex and race",* and *"[the development] of appropriate hypermobility cutoff levels that accurately portray any group differences".* In other words, and in the light of what has been explained above, a cutoff score of 3/9 on the Beighton scale for instance could seem more appropriate for a Caucasian middle-aged male, while a cutoff score of 7/9 on the same scale could suit more to an Asian young adult female. They support this method of differentiated cutoff levels by notably quoting a 1992[46] and a 1996[65] studies, where different cutoff score were applied to individuals of varied age, sex and race in order to incorporate or exclude them of cohort studies about hypermobility.

3.3.3. An appraised prevalence of hypermobility syndromes in the general population…

The most honest assertion regarding the distribution of HMS in the general population is certainly the one made by Beighton et al. in their 2012 reference book

about hypermobility of joints, who, speaking of its prevalence amongst adult, state that *"the true prevalence of JHS in the community is unknown"*[18]. But as mention Grahame (a co-author of the book) and Hakim in another publication, "*[HMS] is believed to be less far common than asymptomatic hypermobility"*[51]. This assumption is supported by Simpson, who in his 2006 review of literature about HMS concludes, regarding its prevalence, that *"generalized joint hypermobility exists without joint pain and doesn't lead necessarily to arthralgia*[*]*"* and that *"patients with hypermobility often lead normal lives and do not have BJHS or another connective tissue disorder"*[58]. Recognizing that the prevalence of JHS remains unknown, Hakim and Sahota in their 2006 publication, nevertheless assumed that *"[it] may lie between 0,75% and 2% in the white population"*. They base this assumption on the determination of a 10% chance of developing symptoms related to hypermobility (thus HMS) made in 2002 by Klemp et al. when studying Maori and European New Zealanders[66]. In the retrieved literature, when speaking about HMS prevalence, the logical assumption was made that its age, gender and ethnicity-related distribution followed the one of polyarticular hypermobility.

3.3.4. …confronted to an underestimated prevalence of hypermobility syndromes in the clinical population

If the alleged numbers for HMS prevalence are true (up to 2% of the general, white population), according to Hakim and Grahame[51], this prevalence would be nevertheless under-estimated in a clinical setting. This feeling is shared by others, notably Bravo and Wolff, who in 2006, demonstrated that 35% of the patients in a Chilean rheumatology clinic had an undiagnosed HMS[67]. Thus, if routinely looked for, HMS is a common finding in clinical population. Simmonds and Keer seem to share the same impression as they write in a 2007 publication[59] *"despite the substantial volume of published literature, JHS continues to be under-recognised, poorly understood and inadequately managed by the medical and physiotherapy professions"*. Taking the extra step, Grahame and Hakim, in 2010 publication, state that on top of being largely neglected, JHS is *"a source of much unrecognised morbidity and unnecessary suffering in the community"*[28].

[*] NDLR, as Remvig et al found in the above mentioned publication, arthralgia is a very reliable minor criteria on the Brighton criteria for HMS

This paradox is perfectly illustrated by the juxtaposition of two studies :

- a 1992 American study conducted by Bridges, Smith and Reid investigated the likeliness of encountering hypermobility in a rheumatology consultation setting and its associated pathological manifestations[68]. On 130 consecutive patients referred to an outpatient rheumatology clinic, they performed routine assessment of hypermobility. They used the Beighton scale with a cutoff score of 5/9 for all of these patients (97 women and 33 men with a mean age of 51 (range 18-83)). They found that 20 (15 %) of these patients presented positive Beighton scores with and average mobility score of 8 (versus ≤ 2 for non hypermobile subjects). All hypermobile subjects were women whereas the total number of referred patients in this clinic was only at 75% feminine. The arousal of symptoms, (notably musculoskeletal) associated with hypermobility fundamentally describing the HMS, we can deduce that the prevalence of HMS in a clinical population could reach 15% (versus the above mentioned 2% in the general population).
- a 2001 British study conducted by Grahame and Bird evaluated the perception of rheumatologists about HMS[54]. They sent a 9 points questionnaire investigating their perception of the HMS (clinic prevalence, criteria for diagnosis, treatments, impact on quality of life…) to the 420 UK-based consultant rheumatologists, members of the British Society for Rheumatology and obtained a response rate of 76 %. Regarding the clinical prevalence of HMS (question : "*approximately how many cases have you seen in the past year ?"*), 49 % of the respondents declared having encountered less than 10 cases over the preceding year. Regarding the impact on HMS sufferers' quality of life (question: *"how do you rate the impact of HMS on peoples' lives in most cases ?"*), 45% of the respondents considered it as minimal. Also, about the correlation between HMS and rheumatic diseases morbidity (question: "*What contribution does HMS make to the overall burden of rheumatic disease morbidity ?"*), 72% of the respondents considered it as minimal. Thus, Grahame and Bird proved with this study that the condition was indubitably under-recognized by the very ones who are the most entitled to diagnose it. It also demonstrated that, although it was essentially reckoned as a distinct clinical entity (92%), the condition was perceived as poorly impacting people's quality of life[*] and as a poor factor of rheumatologic morbidities[**]. As Grahame wrote concomitantly in another publication about HMS[29]: "*It is a paradox that this is the one*

[*] denoting a certain scepticism of the profession towards the symptoms
[**] surprisingly, when one know about the first definition of BJHS by Kirk et al

member of the group [HDCTs] that is the most likely to be overlooked, its manifestations and implications passing undetected" Finally and as it will be discussed in another section of this review, the study demonstrates an overall poor management of the condition, which Grahame and Bird even qualified of *"therapeutic nihilism"* (for instance, 56% of the respondents notably considering that reassurance only was very effective). In the same concomitantly written (but published earlier) publication mentioned above[29], Grahame portended these results writing about HMS patients "*[They] are often told that they have another (more serious) rheumatic disease (and are therefore treated inappropriately) or, worse still, that they have no disease and that their symptoms are trivial, exaggerated or even imaginary. "your joints move well, there is obviously nothing wrong with them (you)" is a commonly heard comment.*"

The comparison of these data, gathered in a priori relatively comparable setting (rheumatology clinics in America and UK) makes one wonder : how come this relatively common disorder is so poorly recognized then ? Surely, as argued Grahame and Bird in their 2001 study about Bristish rheumatologist's perception of HMS, *"the only logical explanation […]is the failure on the part of many consultants to recognise the presence of hypermobility in their patients".* Because as argue Fikree et al. in a 2013 publication[69], *"early estimates suggest that [JHS] may be the most common of all rheumatological disorder".* So how come trained specialists could miss what they surely have been taught to detect and, on top of that, what is so common ? In two other publications solely written by him[22,39], Grahame gives a hint of an explanation, arguing in the latter that "c*onventional wisdom has always favoured the view that "common" hypermobility merely represents the upper end of a Gaussian distribution of the "normal" range of movement. [But] this variety of hypermobility, at least as far as it is seen from the clinic, [could] represent a departure from "normality"".* Rheumatologists would thus confuse a mere pathological feature (joint hypermobility) with a non-significant (or thought so), yet elevated value of ROM. Yet it seems unfair to solely "blame" the medical corps for this under-recognition; patients, because of the profusion of afflictions they suffer from (see 3.4.), often adopt a "migrating behaviour" seeking from specialist to another the best relief they can find[3]. Though, an early diagnosis would present an non-negligible advantage in terms of prevention of further degradation of the patient's states. As simples measures as life-style adaptations, and activities modifications would help in preventing the onset of at least other

musculoskeletal disorder, which HMS sufferers are particularly prone to[58]. In conclusion to these facts, and as Grahame and Bird base their hopes in their 2001 study, the Brighton criteria could be of assistance to clinicians and researchers in the recognition of HMS.

3.4. Symptomatology: clinical manifestations associated with hypermobility and the hypermobility syndrome.

3.4.1. Foreword

As we have previously demonstrated, over the last forty years or so, the definition of the HMS, as first introduced by Kirk et al. in 1967, has shifted from a mere rheumatological disorder to a multisystematic, hereditary affliction of the connective tissues matrix. Concomitantly and despite the demonstration of its non-life-threatening character, the soon argued benignity of the condition has been called into question by several authors[70,71,72]. The origin of the controversy fundamentally lies in the *"increasing number of studies highlighting JH as a predisposing factor and/or non-casually associated features for a series of extra-articular disorders"*, as Castori terms it in his 2012 publication[3]. Indeed, the more JH has been investigated, the more the pervasive and insidious character of the causative HDCT has been unveiled and its impact on patient's quality of life apprehended[73]. Providing us with a contemporary outlook on HMS, Castori tempers these developments by writing that, "*At the moment, whether these complaints belong to the wider picture of the JHS/EDS-HT or rather represent non-syndromic associations needs further investigations"*[3]. Namely, if JH is perceived as "the tip of the iceberg" of an HDCT, the extensiveness of pathological expression of this HDCT remains uncertain and the actual definition of HMS appears nothing less that thorny. Yet for the clarity of this review, we will retain the following fomulation, stemming from Castori and who qualified HMS in 2012 as *"an HDCT with predominant rheumatologic manifestations, [possibly] widespread […] with reverberations in practically all organs and systems"*[3].

That being said, the retrieved generalist literature about the clinical manifestations associated with JH*, provide the reader with a long list of attributes and afflictions[3,18,31,2,28,29,51,57]. Indeed, HDCTs are known to most significantly affect four systems: integumentary, musculoskeletal, ocular and cardiovascular. But as they are caused by defective protein synthesis _which can be varied and sometimes opaque_, their pathological expression (logically depending on the underlying defect(s)), can differ in the extent, way and system which is primarily affected[34]. In the case of HMS, one has to remember that it is a relatively "new" syndrome, which remains, according to the insiders, poorly-understood and under-recognized by the medical corps ; henceforth the actual trend is by and large at the screening trial. Pathological findings but also specific bodily features (i.e. non-pathological strictly speaking) have thus been commonly observed in hypermobile subjects, hence the clinical spectrum associated with JH appears extremely wide.

Ranging from respiratory disorders to psychiatric ones, the clinical manifestations are classified according to different schemes. Some authors choose to distinguish articular (or musculoskletal*) and non-articular (or extra-articular) associated symptoms, while others prefer to classify them according to the body system which is affected, sometimes adding here and there other unclassifiable features. Jeopardizing even more the process of classification is the strong influence of the time (i.e. senescence of tissues, exposure to environmental factors…) on the onset of hypermobility-related disorders, but also the individual susceptibility to its overall deleterious influence[74]. JH in children has been associated with a variety of pathological manifestations for which a strong suspicion of causality exists[72]. And as the disorders often commence in childhood or adolescence, they continue into adult life, with different forms or severity[2]. Ensuing this observation, an innovative classification is made by Grahame and Hakim, who instead of recalling a list of disorders, name some of them according to their likeliness of appearance and more or less big impact of the HMS through the patient's life[28].

In the light of what has been said, it appears unattainable to provide the reader with an accurate and exhaustive list of the clinical manifestations associated with joint hypermobility. Some of them are indeed still being debated while other will likely be

* or better saying and as we explained above, of-the-possible-disorders/characteristics-displayed-when-one-presents-JH,

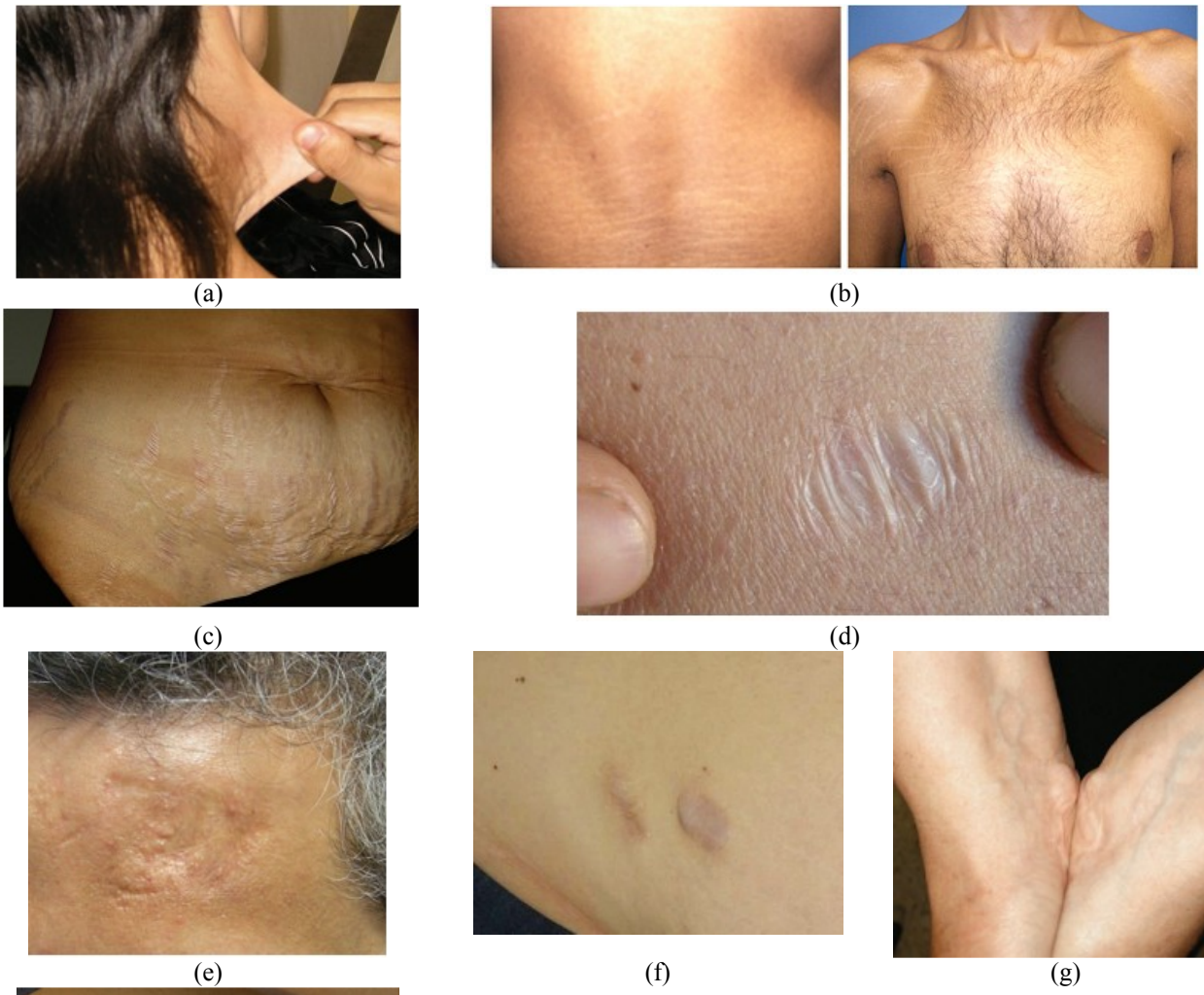
* echoing yet broadening the first definition of Kirk et al

put forward with the increasing comprehension of the underlying pathological mechanisms of the HDCT. The clinical presentation of HMS yet remains extremely variable and profuse. Eluding the question of children and/or preadolescents-specific signs and symptoms (as this population is not within the scope of this thesis), we propose in this section to recount the characteristic and frequently reported symptoms during adulthood. We will not restrict the classification to a bare enumeration of affected systems, as HMS can be represented to a more or less pathological degree in virtually any of them. This would only emphasise the multisystemic character of the disease, which has already been developed earlier. Instead, retaining the classical classification between extra-articular and articular disorders we will elaborate upon it and outline the underlying possible aetiology.

3.4.2. Non-pathological or benign manifestations associated with tissue fragility : cutaneous, mucous, ocular and global morphological signs

It is interesting to notice that a large collection of the signs which have been described in the retrieved literature can be recognized during a standard interview with clinical aspection[67]. Moreover, as Keer and Butler, speaking of the examination of hypermobile patients, notice: *"observation of the patient's mannerisms and postures during history-taking may give an indication of hypermobility"*[75]. If the combination of signs can lead the examiner to suspect HMS, only some of them serve to the diagnosis of HMS[52] and/or EDS-HT[26]. These external signs, directly observable and/or easily accounted for in adult hypermobile subjects, are not strictly speaking pathological. And yet, their accumulation in the same individual and their association with hypermobility (when sought for) characterises somehow a certain phenotypic expression of connective tissue proteins involvement[76].

As mentioned above, the integumentary system involvement in HDCT is characteristic. Although less spectacular in HMS than in other HDCT[57], minor skin defects linked with tissue (i.e. skin) fragility can be observed. Through the literature is primarily mentioned skin hyperextensibility (which demonstration can be as crude as asking the patient to pull a fold of skin on the dorsum of the hand). The skin laxicity is nevertheless less important in HMS than in other HDCT. The skin is also mentioned to



Miscellaneous skin features of HMS :
(a) skin hyperextensibility
(b) abnormal striar across the lower back and shoulders
(c) extensive abdominal striae atrophicae in a 35 years old multipara
(d) atrophic, nonpapyraceous scar
(e) depressed scar
(f) postsurgical scar with anetoderma-like herniation of the subcutaneous fat
(g) piezogenic papules at wrists after compression
(h) keratosis pilaris in a 26 years old woman

Picture 6 (a) to (h) - Miscellaneous skin features of HMS, adapted from *Ehlers-Danlos syndrome, hypermobility type; an underdiagnosed HDCT with mucocutaneous, articular, and systemic manifestations* by Castori, 2012 and *Joint hypermobility and skin elasticity: the HDCTs* by Hakim and Sahota, 2006

be *"smooth and velvety"*[26] for EDS-HT and with possible "*striae, hyperextensibility, thin[ess] or abnormal scarring"* for HMS[52]. The striae (rubrae or distensae), also termed as stretch marks, typically appear around puberty at places affected by growth spurts but also extensor surfaces (elbows, knees)[57]. Abnormal scarring is caused by poor wound healing and translates into atrophic scars, non papyraceous scars, depressed scars or the presence of anetoderma-like herniation of subcutaneous fat on postsurgical scars.

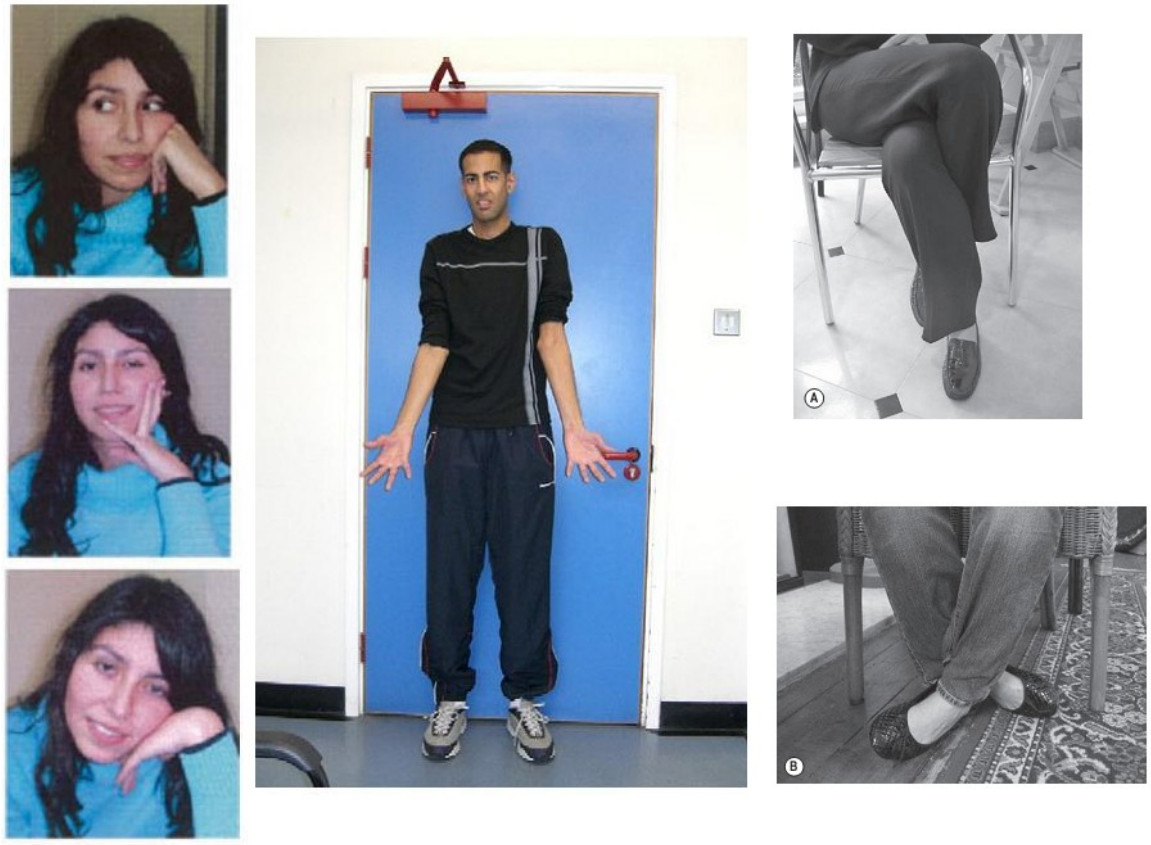
It is particularly observable in sites exposed to repreated trauma such as knees and elbows[3]. Hernias, which also constitute a minor diagnostic criteria of BJHS, can be seen under the form of piezogenic papules namely spontaneous fat herniations through a defective dermis, on heels or wrists, or inguinal, crural, umbilical, epigastric hernias, especially in conjunction with obesity or pregnancy. More rarely, small muscle herniations at sites of discrete areas of incontinent perimysium are observable[3].

Picture 7 - Typical facial characteristics of JHS, reproduced from *Clinical study of HDCT in a Chilean population*, by Bravo and Wolff, 2006

Castori, in his 2012 publication, adds possible ways in which the integumentary system can be affected : cutis laxa, is said to be also observable at a higher rate in HMS patient, but as a late consequence of the skin fragility, and thus in older individuals. This skin loosening is caused by a reduced dermal resistance to extreme soft tissue tensions such as pregnancy or repeated gain and losses of weight. Also, conjectures have been made of the higher frequency of occurrence of keratosis piloris, namely dead skin cells building up around the hair follicle, but are yet to be proven[3]. It is possible to mention here another sign, which although pertaining rather to the cardiovascular system, is observable directly on the skin : the presence of varicose veins[52]. It is to be linked with the capillary fragility which also favours easy bruising[57] but also nose bleeding (epistaxis) and gingival bleeding[77].The affliction of mucus membranes, linked also to tissue fragility can be quoted with other miscellaneous anomalies, them too

easily observable : focal blue purple discoloration of the oral muscosa, minor pigmentation of the enamel (even in the absence of environmental causes (e.g. smoking)[3].

The ocular system is also characteristically involved in EDS, OI and MFS, and the same is true for HMS : blue sclera is also argued to be overrepresented in HMS patients[3,57]. Besides, a collection of ocular anomalies can be found in HMS patients, and although they are not directly observable by the common examiner, a clue to their presence lies in the wearing of glasses or lenses by the patient. A 2012 study investigating ocular anomalies in HMS patients found that xerophtalmia (dry eye syndrome), steeper corneas, pathologic myopia, vitreous abnormalities were present more often in hypermobile subjects than non-hypermobile ones. They also noted a higher rate of minor lens opacities[78].



Picture 8 - Other miscellaneous morphogenic traits of JHS : "hand holding the head sign" (left), Marfanoid habitus (middle) typical sitting posture with legs round each others and resting on the lateral border of the feet (right), reproduced respectively from from *Clinical study of HDCT in a Chilean population*, by Bravo and Wolff, 2006, *Joint hypermobility and skin elasticity: the HDCTs* by Hakim and Sahota, 2006 and *Physiotherapy and occupational therapy in the hypermobile adult* by Keer and Butler, 2010

Defective cartilage and overall tissue fragility does not give rise as one could think only to musculoskeletal disorders; its actuality can also be directly observed: the

Brighton criteria name the antimongoloid slant, and the drooping eyelids (lid laxity)[51] as minor criterias for HMS[52]. In their 2006 study conducted on a Chilean, mostly female population, Bravo and Wolff[67] outlined the existence of typical physical traits in HMS subjects : nasal cartilage abnormality, atypical ears, typical face shape. Castori adheres to this finding, adding that, *"the generalized congenital capsuloligamentous laxity [NDLR seen in HMS] influences the late stage of morphogenesis, which start during foetal age and extends much beyond birth. Mechanical stimuli such as gravity, uterine constraint, and muscle contraction, on growth and modelling of the skeleton are likely more effective in a body with lax joints For this reason, a series of orthopedic dysmorphisms and minor variants usually converge in the JHS/EDS-HT patient and often depict a recognizable pattern"*[3]. Counting what he terms as othopedic dysmophisms rather as pathological articular signs (see 3.4.3.), he mentions notably the leptosomic built (i.e. small bodily frame and a slender physique), a high-arched or narrow palate or again, a facial asymmetry of mild degree, which would likely be secondary to deformational positional plagiocephaly in the neonatal age. The possible physical presentation of a HMS subject would thus not be limited to the marfanoid habitus described in the Brighton criteria, but other features could be observable. Their detection would lie in the attentive observation of the patient. Bravo and Wolff for instance describe in these same patient the frequent occurrence of the "hand holding the head sign" (marked flexion of the metacarpophalangeal and wrist joints and hyperextension of the fingers with holding the head during the interview)[67].

3.4.3. Pathological manifestations associated with tissue fragility: neuromusculoskeletal signs, emphasis on nerve compression syndromes

3.4.3.1. Neuromusculoskeletal symptoms in the hypermobility syndrome

The HMS can be defined "*as a complex mix of acute, recurrent or recalcitrant, widespread soft tissue lesions of traumatic origin, recurrent joint subluxations and/or dislocations, often commencing in childhood or adolescence and continuing into adult life"*[2]. And as Hakim and Grahame outline "*what set HMS patients apart [NLDR: from*

other rheumatology patients] are the unusual frequency, range and number of lesions at any one time or over the life span of the patient"[51]. Those afflictions are, in most cases, attributable to the tissue laxity and/or fragility of the collagen rich structures, namely ligament, skin, cartilage, bone, vascular tissues and myofascial supporting structures (pelvic floor, abdominal wall…)[18].

The involvement of the musculoskeletal system, henceforth of the locomotor systemand, is thus the primary hallmark of the pathological expression of hypermobliity. This feature is conveyed in the diagnostic criteria of HMS. The Brighton criteria does indeed reckons the presence of arthralgia, spondylosis, spondylolisthesis/spondyloslysis, dislocations, subluxations in several joints, soft tissue rheumatisms, e. g., epicondylitis, tenosynovitis, bursitis and uterine or rectal prolapse amongst other participating _but not mutualling excluding_ criteria for the diagnosis of HMS[52]. If one goes with the trend of reckoning HMS and EDS-HT as the same pathological entity, the description of the possible musculoskeletal afflictions is completed by the presence of joint dislocations and chronic joint/limb pain according to the Villefranche criteria[26].

Acute or traumatic :
Sprains (notably recurrent ankle sprains)
Meniscus tears
Acute or recurrent dislocations / subluxations of the :
- shoulder
- patella
- metacarpophalangeal joint
- temporomandibular joint
Traumatic arthritis
Bruising
Fractures
Chronic or non-traumatic:
Soft tissue rheumatism
- tendinitis
- epicondylitis (tennis elbow, golfer's elbow)
- rotator cuff syndrome
- synovitis
- bursitis
- baker cysts
Chondrolmalacia
Temporomandibular joint dysfunction
Nerve compression disorders (carpal tunnel, tarsal tunnel, acroparesthesia, thoracic outlet syndrome)
Spinal pathology :
- back pain
- loose back syndrome
- disc prolapse
- pars defects
- spondylosis, spondylolisthesis
- spinal anomalies, scoliosis, kyphosis
- sacroiliac joint instability
Flat feet and sequelae
Unspecified arthralgia or effusion of foot, ankle, knee, hip, back, neck, shoulder, elbow, wrist or fingers
Osteoarthritis
Congenital hip dislocation
Fibromyalgia

Table 7 - possible neuromusculoskeletal signs for individuals with HMS, modified from *Hypermobility syndrome*, by Russek, 1999.

Yet it appears that this description can remain in the reader's mind rather abstract and it seems that the full range of the possible afflictions and signs does not show through these diagnostic criteria. As recalls Simmonds and Keer in a 2007 review, signs of the locomotors apparatus

involvement can be as crude (and sometimes harmless) as the report of "*stiffness, feeling like a 90 years old, clicking, clunking, popping [of joints], subuxations, dislocations, instability, feeling that joints are vulnerable"*[59]. Compiling serial studies, Russek in a 1999 review manages to give her reader a better idea of the larges possibilities of neurmosculoskeletal afflictions[1]. They are presented in the table 7.

3.4.3.2. The occurrence of nerve entrapment syndromes as a clinical sign of pathological joint hypermobility

Ensuing this thorough listing of neuromusculoskeletal disorders correlated with hypermobility, let's get to the heart of the matter, namely its association with compression neuropathies, and ergo disclose our topic of interest. If Russek unequivocally names nerve entrapment syndromes (NES) as hypermobility-related disorders, the same can't be said about the very official Brighton criteria. The latter _which, as stated before, serves as the major diagnostic tool for HMS_ does not mention anywhere NES as minor or major diagnostic criteria… Or as matter of fact, it might does… but only in a concealed manner: under the label "soft tissue rheumatisms". This nebulous denomination, interchangeably used with theses of "soft tissue disorders", "soft tissue rheumatic disorders" or again "soft tissue lesions", gives rise to confusion. In some authors minds, and accordingly with the World Health Organisation's international classification of diseases (WHO-ICD-10), it pertains solely to the "*afflictions of the musculoskeletal system and connective tissues*" (M00-M99). NES are for their part confined to the neurologic section, in the *"diseases of the nervous system"* (G00-G99)[79]. Russek[1] but also other authors[3,58] appear to follow this classification as she distinguishes nerve compression disorders from soft tissue rheumatisms. However, different authors, and notably noted authorities on the topic, seem to consider things differently. In their 2012 book, "hypermobility of joints", Beighton et al. mention in a few lines NES as disorders which have been associated with hypermobility. At this occasion they catalogue NES as soft tissue lesions, along with tennis and golfer's elbows or again, adhesive capsulitis. One has to remember that the 1998 revised Brighton score has been published under the names of two of these

very same authors (Grahame and Bird). Thus, whether the Brighton criteria implicitly include the occurrence of CN as a minor criterion of HMS remains unclear. It is nevertheless our opinion that, in many care-givers' minds using the Brighton criteria, the minor criteria "soft tissue rheumatism" does not include NES. Yet, despite the confusion around the criteria for diagnosing HMS, the HMS treatment-targeted literature retrieved seem to include NES as a manifestation of pathological joint hypermobility, probably based on clinical experience or rather out of convenience. The fact remains that in doing so, they label individuals who display JH and suffer from NES as a HMS sufferers.

Now examining the very nature of the correlation between JH/HMS and NES, we propose to analyze the available literature, starting with an authoritative source on this topic, the "hypermobility of joints" entitled book, written by Beighton et al. and published in 2012. Its authors state that, *"entrapment neuropathies may [...] occur in relation to hypermobile joints. Examples include the carpal and tarsal tunnel syndromes, common peroneal and sciatic nerve compression"*[18]. Surprisingly enough, those two lines constitute the only consecrate part of a 219 pages-long book dealing with JH, to its connection with NES. If we exclude two other laconic comments on NES[*], the processing of the topic appears nothing less than meagre, not to say disappointing. In another reference book written by Hakim et al and published in 2010, the mention of NES appears less anecdotal but just as much compendious. Specifying the symptomatology of HMS, the authors assert that "*it is not surprising [...] that entrapment neuropathies are found to be more common in JHS"* as, as they argue just before, *"peripheral nerves are vulnerable to trauma when their path takes them round wide-angled bends. The risks are increased when the angles are exaggerated by hypermobility"*[80]. This scarcity however seems in line with the low amount of publications dedicated to this topic: between 1987 and 2013, a dozen of studies linking in some manner JH/HMS and NES have been published[70,81-91]. Their results, complementing the picture that has given us Russek before, are presented in the form of a table on the next page and discussed below.

[*] on the peculiarity of the incidence of compression neuropathies (since the pathology occurs at distance of the joint), yet argued to be long recognised, and on their possible disturbing effect on sleep cycle and involvement in chronic fatigue syndrome.

Table 8 - Mention of nerve entrapment syndromes in correlation with hypermobility or joint hypermobility syndrome in the literature between 1987 and 2013.

Publication			Study objectives, research topics	Studied population				Diagnostic methods employed for JH/ HMS/ EDS-HT	Hypermobile population			Occurrence of nerve entrapment syndromes and related conditions amongst JH patients	Main results
Date	Authors	Type		Place	N	G	A		N	G	A		
1987	Francis, March, Terenty[81]	Prospective study	Signs and symptoms associated with TTS	Rheumatology department (Australia)	11	- 9♀ - 2♂	- MA : 43 - R : 13-72	Beighton score ≥3/9 (mean value 6 /9)	9 (81%)	- 9♀	- MA : 43 - R : 13-72	- TTS : 9 (81%)	- tripartite association between HMS, TTS and flat feet (mobile or rigid) in 81% of the patients
1988	March, Francis, Webb[82]	Cases reports	Mechanisms by which JH can cause NES	Rheumatology department (Australia)	4	- 3♀ - 1♂	- MA : 30 - R : 24-37	Beigthon score ≥6/9 (mean value 7,5/9)	4	- 3♀ - 1♂	- MA : 30 - R : 24-37	- CTS : 3 (85%) - CPNP+ sciatica : 1 (25%)	- CTS caused by deleterious sleep posture enhanced by HMS - sciatica and CPNP caused by prolonged deleterious sitting position enhanced by HMS
1989	Patrone, Hoppman, Whaley[83]	Cases report	Hypermobility leading to fifth digital nerve entrapment	Medical performing arts clinic (USA)	1	- 1♀	- 19	Clinical examination (revealing hypermobility of hand joints)	1	- 1♀	19	- DNC : 1 (100%)	- fifth finger DNC caused by dislocation of metacarpophalangeal joint
1990	Rovetta, Bianchi, Monteforte[84]	Cases reports	Mechanisms by which JH can cause CTS	Rheumatology centre (Italy)	7	- 5♀ - 2♂	- MA : 32 - R : 21-48	Beighton score ≥5/9 (mean value 7,1/9)	7	- 5♀ - 2♂	- MA : 32 - R : 21-48	- CTS : 7 (100%)	- CTS in the absence of tenosynovitis, caused by increased tendency to oedema correlated to synovial hypermobility
1991	Bell, Chalmers[85]	Case reports	Association of EDS-HT and CPNP	Orthopaedic hospital (Scotland)	1	- 1♀	- 25	NS	1	- 1♀	25	- CPNP : 1 (100%)	- recurrent CPNP possibly caused by tomaculous neuropathy, direct mechanical trauma or repetitive traction injury
1991	El-Shahaly, El-SHerif[70]	Prospective study	Signs and symptoms associated with BJHS	Rheumatology rehabilitation unit (Egypt)	114	- 95♀ - 19♂	- MA : 33,2 - R : ±15,6	Beighton score ≥5/9	114	- 95♀ - 19♂	- MA : 33,2 - R : ±15,6	- acroparesthesias (hand, feet or both) : 66 (57,9%) - CTS : 36 (61,6%) - TTS: 16 (14,0%) - CTS + TTS : 14 (12,2%)	- high percentage of upper and lower limb paresthesias, CTS, TTS and combined CTS and TTS in HMS patients
1995	Gallan, Koussef[86]	Cases reports	Association of EDS-HT and BPP, LSPP	Paediatric department (Spain)	2	- 2♂	- MA : 12 - R : 6-18	NS	2	- 2♂	- MA : 12 - R : 6-18	- BPP + LSPP: 1 (100%) - BPP: 1 (100%)	- idiopathic BPP and post-traumatic (fracture) BPP on the EDS-HT
1995	Hudson, Starr, Esdaile[87]	Prospective controlled study	Signs and symptoms associated with BJHS	Rheumatology department (Canada)	378	- 282♀ - 96♂	- MA : 52,3 - R : 16-85	-Beighton score (46 diagnosis of JH) - Bulbena criteria (42 diagnosis of JH)	50 (13,2%)	- 47♀ - 3♂	- MA : 45,5 - R : 16-72	- TOS (symptoms): 27/46 (54%) - TOS (diagnosed) 13/46 (26%)	- 54% of suspected TOS amongst hypermobile patients and 26% of diagnosed TOS amongst hypermobile patients
2002	Ghossoub, Tebet, Faraj[88]	Prospective study	Outcome factors in rehabilitation of TOS	Physical medicine service (Lebanon)	85	- 71♀ - 14♂	- MA : 34,5 - R : 18-66	NS	36 (42,5%)	NS	NS	-TOS with ligament hypermobility: 36 (42,5%) - TOS with ligament hypermobility, family form: 4 (5%)	- 42,5% of TOS patients have hypermobility - hypermobility plays a negative role in immediate outcomes of TOS physiotherapy
2008	Aktas, Ofluoglu, Albay[89]	Prospective controlled study	Assocatoin of BJHS and CTS	Physical medi-cine and rehabi-litation depar-tment (Turkey)	90	NS	- MA : 45,8 - R : ± 10,4	- Brighton criteria	55 (61,1%)	NS	- MA : 49,5 - R : ±10,8	- total BJHS distribution: 54 (60%) - non CTS group: 7 (20%) - CTS group: 47 (85%)	- 85% of BJHS in CTS patients versus 20% of BJHS in non CTS patients - BJHS is a predisposing factor for CTS
2009	Voermans, Van Alfen, Pillen[90]	Comparative study	Neuromuscular features in various types of EDS	Neuromuscular centre (Netherlands)	40	- 31♀ - 9♂	- MA : 35,2 - R : 14-63	- serum analysis showing TNXB haploinsufficiency	20	- 16♀ - 4♂	- MA : 36 - R : 20-62	- CTS: 1 (5%) - CPNP: 0 (0%)	- abnormal nerve conduction in 9 (45%) - CTS in 1 (5%) - extracellular matrix defect in peripheral nerve
2013	Granata, Padua, Celletti[91]	Prospective controlled trial	NES and polyneuropa-thies in JHS/EDS-HT	Physical medi-cine and rehabi-litation depar-tment (Italy)	30	- 26♀ - 4♂	- MA : 32,8 - R : 15-58	- Brighton criteria for HMS - Villefranche criteria for EDS-HT	15 (50%)	- 14♀ - 1♂	- MA : 35,4 - R : 15-58	- paresthesias, numbness of the hand : 12 (80%) - paresthesias , numbness of the sole of feet: 3 (20%) - cramps of the lower limbs : 13 (86,7%) - CTS : 1 (6,7%) - UNE : 1 (6,66%)	- higher rates of luxations and subluxation of the ulnar nerve in EDS-HT patients - possible hyperlaxity of the Osbourne ligament, possible altered nerve stroma, possible subdiagnostic involvement of peripheral nerves

A: age (years old) – BJHS: benign joint hypermobilty syndrome – BPP: brachial plexus palsy – CTS: carpal tunnel syndrome – CPNP: common peroneal nerve palsy – DNC: digital nerve compression – EDS-HT: Ehlers-Danlos syndrome, hypermobility type – **G**: gender – HMS: hypermobility syndrome – JH: joint hypermobility – JHS: joint hypermobility syndrome – LSPP: lumbosacral plexopathy – **MA**: mean age (years old) – **N**: number – NES: nerve entrapment syndrome – **NS**: not specified – **R**: range TOS: thoracic outlet syndrome – TTS: tarsal tunnel syndrome – UNE : ulnar nerve entrapment at the elbow

The literature dealing with both JH/HMS and NES consists mostly of case reports (thus with very little level of evidence) and prospective studies. As mentioned above, it also appears very scarce. We can observe that, at the exception of the ones of Francis et al. in 1987, Ghossoub et al. in 2002, and Aktas et al in 2008, all the publications were primarily focussing on JH/HMS or EDS(-HT) rather than on NES. Besides, they present with several shortcomings notably in terms of study samples (population size, nature…) and diagnostic means. Indeed, the studies were overall conducted on a clinical population, primarily rheumatologic and feminine one. On the other hand, the diagnostic methods employed either for JH/HMS/EDS-HT or NES appear disparate and not of the same reliability. The diagnosis of nerve entrapment was primarily made through the patients' clinical examination and provocative manoeuvres (Adson's test, Tinel sign…) and eventually confirmed with electrophysiologic studies; only Granata et al in 2013 also performed dynamic ultrasound evaluation. Regarding the hypermobile status of patient, it is the diagnosis of generalized joint hypermobility that was primarily established with the use of Beighton scale; only Aktas et al. and Granata et al. chose to use the Brigthon criteria for the diagnosis of BJHS, confirming the poor use which is done of this diagnostic tool. Other researchers simply mentioned an underlying EDS-HT without specifying their means of diagnosis. It has to be noticed that in the case of the study of Voermans et al., the researchers argued that the EDS-HT patients could be diagnosed as such because of a reduced serum level in tenascin caused by TNXB haploinsufficiency (namely with only one single functional allele of the TNXB gene); in parallel, they distinguished a group of TNXB-deficient patients from the aforementioned EDS-HT ones[**]. It is thus necessary to ponder the global level of evidence that is provided by these studies' results. They nevertheless provide us with substantial information regarding the types of NES correlated with JH/HMS/EDS-HT and the nature of this link.

Regarding the types of NES which have been correlated with JH/HMS or EDS-HT, it is first important to remember, as we mentioned at the beginning of this work, that there exists about 50 different NES. They are the result of a compression of a vascular and/or nervous structure at the level of bony, fibrous, osteofibrous or fibromuscular tunnels and affect either the upper limb, the lower limb or even the trunk[6].

[**] we consider, with regards to what we will explain later about the aetiology of HMS, that EDS-HT, TNX-deficient type EDS and HMS patients can be assimilated in a same group.

According to our retrieved studies, only 7 types are found to occur in correlation with hypermobility: the TOS/brachial plexus palsy, the ulnar nerve entrapment, the CTS, the digital nerve compression, the sciatica, the CPNP and the TTS. It is interesting to notice that some of them are undeniably more commonly found amongst the general population than others, and for instance, the CTS is thought to be the NES with the highest prevalence (close on 4%) amongst the general population[92]. Logically, CTS is also the most reported of NES affecting the hypermobile population. But is important to notice that the rate of hypermobile patients affected by certain types of NES appears extremely high in comparison with the general population: El-Shahaly and El-Sherif found that amongst 114 hypermobile patients, 31,6% presented CTS and 14 % presented TTS. For the TOS, Hudson et al. mentioned a rate of 26% of actually diagnosed ones in hypermobile patients and Ghossoub et al. found a proportion of 42,5% of TOS patients presenting ligament hypermobility (yet 5% only presenting what they called the family form).

What is also striking is the simultaneous and/or repeated occurrence of different NES in hypermobile patients: El-shahaly and El-sheriff reported that TTS commonly occurred jointly with CTS in hypermobile patients (12,3%). March et al. described a patient presenting both a sciatica and bilateral CPNP in the absence of a widespread peripheral neuropathy. Galan and Koussef presented the case of a young man, diagnosed with EDS-HT and who presented consecutively recurrent brachial plexus palsies and lumbosacral plexopathy. Likewise, acroparesthesias seem to be common in hypermobile patients: Rovetta et al. reported that all of their hypermobile patients presented acroparesthesias evolving for 6 to 45 months and in which treatments (surgery or corticosteroids injections) were unsatisfactory. El-Shahaly and El-sheriff report it occurring in 57,9 % of their hypermobile patients, and stated that it is frequently accompanied by brief periods of morning stiffness of the fingers or pain along the entire sole at the first step. Similarly, Hudson et al. noticed that *"symptoms suggestive of TOS were reported commonly in this group of patients (54%)"*. And recently Granata et all attributed upper limb paresthesia (80%) and lower limbs parasthesias (20%) and cramps (86,7%) to a possible subdiagnostic involvement of the peripheral nervous system in a series of 15 EDS-HT.

Regarding the profile of patients affected by both ailments, authors however do not agree on the most likely age of onset for NES correlated with HMS : Rovetta et al.,

Galan and Koussef seem to think that they would rather occur at a young age. El-Shahaly and El-Sherif to the contrary notice that hypermobile patients affected by NES were significantly older than the ones who did not present NES. Finally, the studies unanimously ascertain that females are the most affected by a conjunction of HMS and NES, as they incidentally are by HMS.

HMS is instinctively thought to be at least a predisposing factor in the onset of NES. For instance, Aktas et al., confining themselves to the strict analysis of numeral data and facing the high proportion of coexisting CTS and HMS in their patients, stated in 2008 that *"BJHS could be a predisposing factor for the onset of CTS or vice versa"*. Most of authors even forbear from mentioning that second possibility of reverse casual relationship probably because of its unlikelihood regarding the pathomechanisms of both ailments. Sporadically, few authors take the extra step by naming HMS as a causative factor for NES and accordingly propose possible pathomechanisms; according to them, nerve compression syndromes would occur within the framework of an underlying hypermobility primarily because of incorrect and detrimental static and/or dynamic postural activities. Orthopaedic dysmorphisms (subluxations, flat feet,…) resulting from generalized joint hypermobility and tissular anomalies have also been put forward :

- **the prolonged maintaining of certain postures (sleeping and sitting notably), enabled by an underlying hypermobility** has been claimed as a primary factor of onset of CTS and TTS and sciatica; in the case of CTS, March et al. found that a sleeping posture with the wrists in hyperflexion, tucked in the armpits sufficed to trigger the symptoms. They also outlined that CTS in those cases could not be the result of an overuse syndrome and that no sign of synovitis could be detected. Questioning about the idiopathic CTS, they argued that this mechanism would be overlooked, considering the high efficiency of night splinting in the management of CTS. Aktas et al, referring to the study of March et al. also argue that night posture could be a mechanism of onset of CTS in hypermobile patients as more than half of their CTS patients had nocturnal paresthesias and pain. March et al. again found that maintaining the lotus posture or non-ergonomical sitting on a chair (with the ischial tuberosities at the edge of the chair) resulted in the onset of CPNP and sciatica. In those cases, it was hypermobility that was making possible the adoption of these postures.

- **detrimental dynamic postural activities**, similarly to static postural ones, could be enhanced by hypermobility and trigger intermittent compression and/or excessive stretch of the nerve resulting in a NES. Indeed, in the case of the brachial plexus palsy displayed by two young EDS-HT sufferers, Galan and Koussef, argue that the excessive stretching of nerve in the area of the shoulder could cause their symptoms. A digital nerve compression occurring in female musician reported by Patrone et al. was attributed to an intermittent dislocation of the metacarpophalangeal joint enabled by JH. This dislocation, occurring only when the patient was playing her instrument, was thought to produce pressure on the digital nerve against the metacarpophalangeal ligament and splinting designed to avoid this dislocation alleviated the symptoms. Bell and Chalmers, describing a 25 years old patient presenting EDS-HT and recurrent CPNP argue that the most likely mechanism, in accordance with the patient's medical history would be a repetitive traction injury as a consequence of the hypermobility of the joint.
- **localised and sequelar orthopaedic dysmorphisms, issued from JH** and associated with altered movement patterns would also play a role in the onset of NES ; Francis et al argue that an increased stretch of the nerve would be enhanced by incorrect mechanics of the foot in the case of TTS associated with JH. It is here the sequelae of JH, under the form of feet deformities (mobile flat feet and hindfoot valgus) that would result in the stretch of the tibial nerve. Along these lines, Hudson et al stated that regarding TOS, ligamentous laxity could be important factor in the anatomical changes resulting in a pressure phenomenon of the thoracic outlet.
- **tissular anomalies of the connective tissues but also of the nervous and muscular tissues** have been put forward as a possible mechanism in the development of NES in correlation with hypermobility by some authors; Logically, altered connective tissues could mechanically impair peripheral nerves for they are found at their direct or indirect contact, especially in at-risk tunnels; Granata et al, examinining a series of 15 EDS-HT patients discovered a high rate of ulnar nerve subluxations and luxations which they correlated to a possible hyperlaxity of the Osborne ligament. The latter could enhance the frequency of ulnar nerve luxation and subluxation at the elbow which would eventually cause recurrent friction between the nerve and the bone. More globally they argue that altered connective tissue could increase nerve tension because of altered nerve stroma, fixating ligaments and tendons. More hypothetically, Rovetta et al. argue that hypermobile patients would have an increased aptitude to the production of a

subclinical (i.e; non detectable) oedema that would result in the median nerve compression in the case of CTS. Voermans et al suggest that the extracellular matrix defect seen in HDCTs (here EDS) affects also the muscular and peripheral nervous tissue. They pointed out a possible JHS/EDS-HT neurologic phenotype with a high rate of myopathic electrophysiologic findings, possibly combined with myopathic changes at biopsy, reduced sensation and muscle weakness.

3.4.4. Miscellaneous other pathological signs possibly associated with autonomic dysfunction : addition to the multisystemic character of the hypermobility syndrome

Our primary interest through this thesis being the question of the onset of nerve entrapment syndromes in hypermobile subjects, symptoms affecting other systems than the locomotor one do not appear to be within its scope. Besides, extra-articular or non-musculoskeltal symptoms, as they are most often termed, happen to be so varied and numerous that it would be impossible to address the topic without showing inaccuracy. Yet, they appear to be worth mentioned for at least two reasons : their recognition in HMS sufferers open the way to new fields of research regarding the pathomechanisms of the disorder but also to new perspectives of management, notably mutlidisciplinary approaches[93]. We will thus tackle here briefly the range of other possible displayed by adult hypermobile subjects, sorting them by the system which is primarily affected :

- endocrine system : amongst the afflictions touching the endocrine system, we can quote the dry mouth syndrome (xerostomia), the dry eye syndrome (xerophtalmia), a perturbed perspiration (excessive or diminished sweating, i.e. diaphoresis and hypohidrosis) and a vaginal dryness. Theses exocrine deregulations could be caused by an underlying dysautonomia according to Castori[3].

- respiratory system : chest pain, shortness of breath have been observed with a higher incidence in HMS patients[94] Moreover, spontaneous pneumothorax[67] and asthma are also considered to be associated with EDS[57,95].

- neurological system : the involvement of the neurologic system in HMS patients only start to be better acknowledged and this increased awareness pertains to the rising evidence of the association of psychiatric disorders in hypermobile subjects[96]; anxiety, panic disorders, agoraphobia and depression have been reported to be more frequent

amongst HMS patients[94,96-99]. Concomitantly to the acknowledgement of higher rates of psychiatric afflictions in HMS patients, arouse the question of the involvement of a dysfunction of the autonomic system, under the form of cardiovascular system deregulations with dizziness light-headedness, presyncope state[94] but also tiredness/sleepiness, chronic fatigue, dizziness, occasional syncope, marked cold intolerance, inability to stand for some time without moving the feet…[67]

- gynaecological : uro-genital prolapse is thought to be the direct consequence of the intrinsic weakness or poor tensile strength in the supporting structures. Pelvic floor weakness may lead to uterine prolapse with reports of a prevalence of hypermobility as high as 40-60%. Hypermobile women would also be suggested to a higher incidence of urinary incontinence[100] and dyspareunia and present an increased susceptibility to urinary infection caused by vesico-urethral reflux[101]. JH may also influence the course of pregnancy and delivery with a risk of divarication of the rectus abdominis muscle and trauma to the vaginal vault and surrounding tissues during labour[102]. Also, the increase of the weight of the uterus during pregnancy, combined with the influence of hormonal factors (e.g. relaxin) result in increase stretch in the surrounding tissues; there is then a greater risk of low back pain and pelvic girdle pain, cervical incompetence and premature rupture of membrane and premature labour and delivery[102].

- gastrointestinal : as Grahame and Hakim mention it in a 2010 publication, *'there is now burgeoning evidence linking functional gastrointestinal disorders with JH and HMS"*[28]. Nausea, stomach ache, diarrhoea and constipation but also bloating, and reflux symptoms with gastro-intestinal dysmotility and irritable bowel syndrome have thus been reported to have an increased incidence in our population of interest. The mechanisms underlying such an extended visceral involvement are obscure; Castori quotes possible contributing factors such as a reduced fixation to adjacent structures causing visceroptosis and hernias, gut hypotonia/ hypomotility and structural anomalies such as dolichocolon[3].

- cardiovascular : early studies have suggested an association between mitral valve prolaspe and HMS but later studies have questioned it because of stricter echocardiographic criteria for this disease[58]. Raynaud's phenomenenon has also been seen at higher rates in hypermobile subjects[103]. If both of these afflictions suggest a connective tissue involvement, the cardiovascular system could also display symptoms caused by a dysfunction of its autonomic regulatory mechanisms such as palpitations, postural orthostatic tachycardia syndrome, mild orthostatic hypotension[94].

We draw the reader attention to the fact that the present listing is far from being exhaustive. If these afflictions are commonly observed in HMS patients, they pertain to an adult population, and do not reflect the range of symptoms observable in children and preadolescents[72], as it is not within the scope of this thesis. As mentioned above, the observation of this wide range of afflictions uncovers possible new pathological mechanisms playing a role in HMS, and notably a dysfunction of the autonomic nervous system. Grahame and Hakim estimate that *"over two third of patients have significant and clearly identifiable autonomic abnormalities"*. These could give rise to psychiatric, cardio-respiratory, endocrine, and gastrointestinal disorders notably and adds to the multisystemic character of the syndrome[28].

3.4.5. Pain as the predominant pathological sign despite the variability of the hypermobility syndrome's clinical presentation

In spite of (or maybe because of) this lengthy description of the possible afflictions presented by HMS patients, remains the impression of a difficulty "characterizable" syndrome. Indeed, if one consider the sole _and utterly consensual_ involvement of the locomotor system, the hypermobility can become symptomatic : (i) at any age (i.e. from early childhood till an advanced age), (ii) in virtually any region of the body (e.g. shoulder, knee, ankle, back…), (iii) with an either isolated or recurrent character (i.e. acute versus chronic) and (iv) under extremely variable pathological forms (e.g. dislocations, fractures, tenosinovitis, tendonitis, osteoarthritis…) .

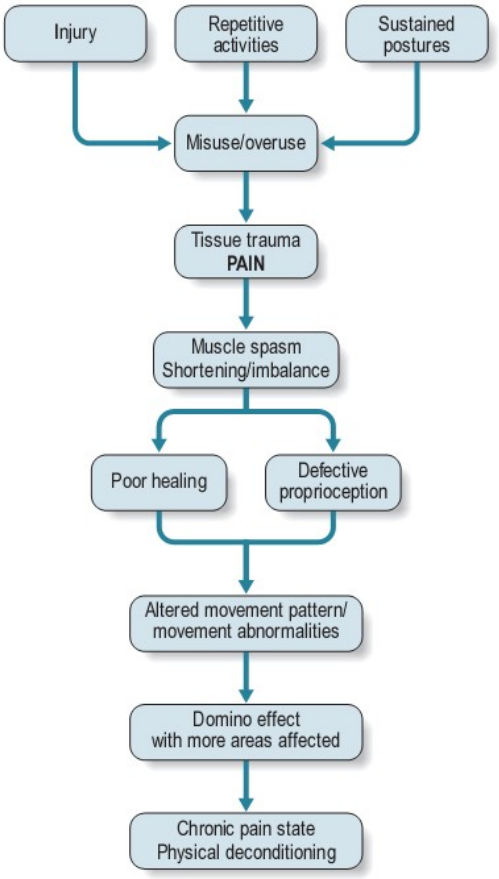
To add to one's justified perplexity, the syndrome, as it is nowadays defined and recognized, does not affect hypermobile individuals to the same extent, henceforth, does not bear the same repercussions on their quality of life. Speaking of the impact of joint hypermobility, Gurley-Green, in a 2001 publication entitled *living with the hypermobility syndrome*[74], divides patients in two broad groups :

- *"Those least affected which may suffer periods of pain and injury, usually lasting several weeks. After effective treatment, they can be relatively symptom-free for some time.*
- *"[Those], who are more severely affected, [and for which] each day is a struggle against pain and injury."*

Yet according to her, a common trait to both groups is *"the deterioration over time [NDLR: and for women, who are more often affected] particularly after pregnancy"*. Outlining the importance of the chronic character of the condition, she adds that *"this is contrary to much in the literature which suggests that symptoms decrease with age. The reported stiffening with age does not always bring less pain. On the contrary, many of our members have increasingly painful symptoms"*. Grahame and Hakim elaborate on this facet of the HMS by dividing the clinical presentation of the syndrome into three tiers[28], form the lesser degree of impairment (first tier) to the most disabling state (last tier) into which patient potentially if no prevention measures are take. Keer and Butler[104] have incidentally summarised this downward spiral into a scheme which is presented below. According to the patient's possible afflictions, they distinguish :

- **the *"musculoskeletal tissue laxity"*-sufferers tier** which comprehends the least severely affected population and thus notably children from any age which can display *"motor delay (omitting crawling and delayed walking), unsteadiness with falling (genu valgum/recurvatum, ankle sprains, flat feet), clumsiness and dyspraxia (e.g. difficulty with ball catching and using scissors) and pains"*. Under the influence of several external factors (e.g. work, sport practise…), this population is likely to develop joint, muscle, soft tissues, spine, pelvic floor, hernias and varicose veins disorder.

- **the *"non-articular"* symptoms-sufferers tier** which comprehends a more severely affected population, in which there was "*no let-up in the barrage of painful events"*. It could concern 24% of the HMS sufferers by the time they seek specialist advice. The range of afflictions comprises "*widespread*



Picture 9 - The downward spiral in the pathological presentation of HMS, reproduced from *Physiotherapy and occupational therapy in the hypermobile adult*, by Keer and Butler, 2010

chronic pain, (due to pain amplification), […leading] to pain avoidance by movement avoidance (kinesiophobia), and severe muscle deconditionning, often significant autonomic dysfunction".

- the *"psychosocial sequelae"*-sufferers tier which comprehends the most severely affected population, , which was not *"rescued from vicious downward spiral"* and for which "*further descent into the third tier of presentation [was] almost inevitable"*. The third tier, estimated to 5-10% of the HMS subjects, is the more impacted in terms of quality of life and access to satisfactory therapeutical management of the condition. In this tiers are found individuals in which the HMS has given rise to anxiety, depression, obesity; work incapacity, isolation, resentment and anger.

As a result of the foregoing, one should not look for unity in the clinical presentation of hypermobility-related signs in a single, but rather in all bodily systems; what is more, pain appears as the one unifying symptom in HMS, the same way hypermobility is the unifying feature of HDCTs. As Gurlet-Green writes, *"Pain is the most common symptom reported to us. For patients it comes in varying degrees, and is often quite unbearable"*[74]. Ensuing this preliminary description, and if pain is the predominant presenting complaint in HMS, it is also ascribed though the literature as :

- either "acute"[51,57], "localized"[51], yet "often recurrent"[51], and can then be secondary to tendon or soft-tissue inflammation, joint degeneration or trauma[57]
- or "sometimes chronic"[51], "progressive"[29], "widespread"[51,59], "frequently diffuse"[1], "longstanding"[59], but also "inconsistent with observed pathology"[1*] and "debilitating"[74] and "feared"[74,105], and can, if unabated and recurrent, evolve into chronic pain syndrome[106], chronic fatigue syndrome or fibromyalgia[57,107]

The pain can also assume different forms, adjoining the sole motive of consultation, notably frequent headaches (especially migraines)[3,29] and intermittent abdominal pains[29]. Complementing this characterization of pain felt by HMS patients, Simmonds and Keer in a 2007 publication[59] propose a *"typical JHS body chart presentation"* (picture 10) which outlines the sites and features of pains experienced by HMS patients. Yet it seems that this description pertains more to an already evolved type of HMS, for which the individuals presenting with such characteristics would be classified in the second or third tier of clinical presentation, as Hakim and Grahame described it.

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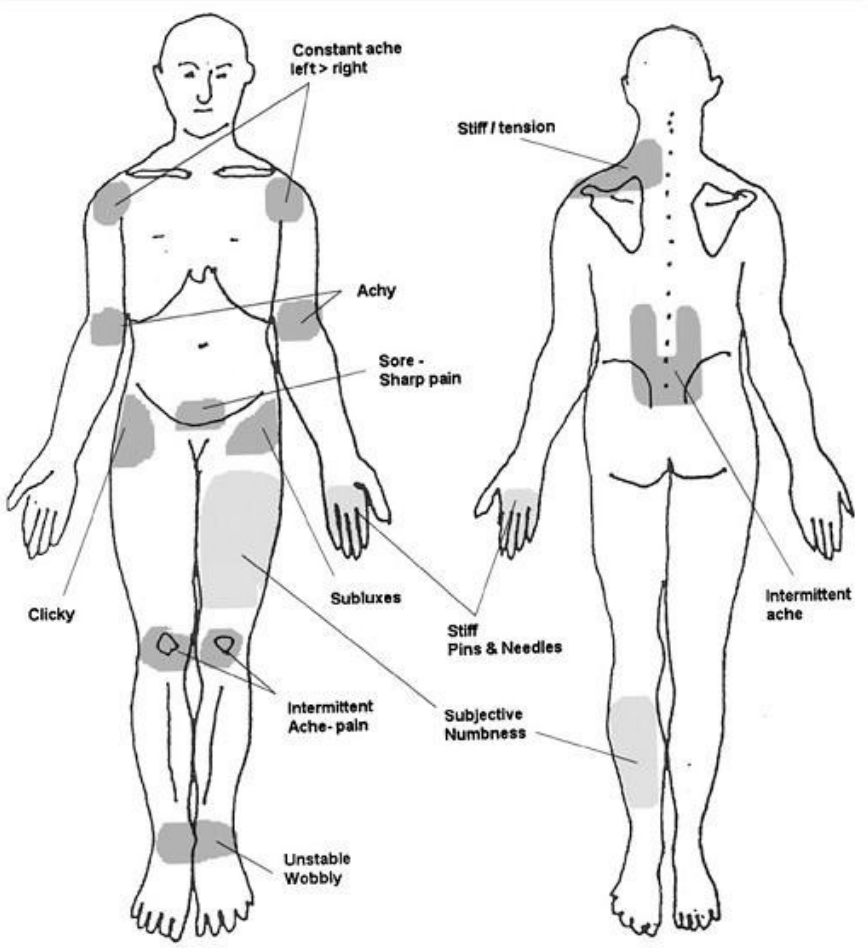
[*] Simmonds and Keer write :"c*omplaints are often difficult to match with the way the patient looks or moves as the individual frequently look well and moves well".*[59]



Picture 10 - Typical body chart presentation of HMS sufferers, reproduced from *Hypermobility and the hypermobility syndrome*, by Simmonds and Keer, 2007.

According to Grahame, several mechanisms involved in the pathogenesis of chronic pain in HMS can be outlined[19] :

- the tissue fragility causing injuries either of traumatic origin or due to overuse; they are frequent, severe and persisting as aggravated by a poor cicatrisation.
- the arthrosis : either localized or diffuse and by definition accompanied by pain, the hypermobility would predispose affected individuals to its onset.
- the associated fibromyalgia: possibly affecting adults but also children and of unknown origin, it has been nevertheless linked to hypermobility, as the clinical features of fibromyalgia, particularly the trigger points are commonly found in HMS patients.
- the psychogenic pain : psychological distress is frequently encountered in HMS patients, notably under the form of depression ; because of its lowering effect on the perception of pain, it could ultimately aggravate it through a vicious circle mechanism.
- a possible widespread neurological defect evidenced by three findings in HMS patients, the resistance to certain types of antalgic medications, and a diminished

proprioception in joints ; moreover, there could be an enhancement of nociceptive inputs from the periphery caused by segmental reflex responses provoked by tissue injury.

This interlocking of pain and HMS potentially impacts the patients' quality of life into various ways and at a great extent ; this is perfectly described by Gurlet-Green who wrote in the same publication[74] : "s*evere HMS can colour an individual's attitude to his or her body and whole life. Life and all activities become linked with pain",* adding a little later that: "*everyday activities of life carry the price of pain; these include brushing teeth, getting dressed, shopping for food, doing the laundry, any repetitive movement, including chopping, typing, ironing and walking, and especially lifting and carrying".* As a logical result, HMS can ultimately bear a very negative effect on the patients' social, work, and sentimental life, which, focussing on the affected female population, Gurlet-Green describes in those terms: *"Holding down a job or looking after a family is often barely impossible. Frequent absenteeism from work due to pain and injury labels the HMS patient as lazy or problematical and may halt advancement at work. It is not uncommon for an HMS patient to have tried several careers. Obviously, with the problems of daily life just outlined, caring for children and running a household is as difficult for an HMS patient as is working in full-time employment. The effect of HMS on the family and relationships can be devastating. Many patients tell me that even being touched can cause them pain. Partners often become frustrated when patients are unable to participate in family activities".*

3.5. Etiology: from the hypermobility genotype to the hypermobility syndrome phenotype.

3.5.1. A strong genetic determinism with widespread biomolecular repercussions

Joint mobility is influenced by several environmental factors, and thus, joint hypermobility can be acquired. At a single joint, the effect of repeated manipulations are thought to increase the likelihood of joint hypermobility[108]; recurrent dislocation of

the shoulder and patella as well as other orthopaedic abnormalities are associated with joint laxity[20,58] and trauma, surgery and regular training (i.e. stretching) may contribute in increasing the range of motion at one or more joint[3,17]. Generalized joint hypermobility as well can result from the exposure to certain factors; certain substances or drugs such as oral contraceptives are suspected to increase female's flexibility, particularly making them more prone to anterior cruciate ligament injury by provoking structural changes in the metabolism of fibroblasts[17]. Some corticosteroids such as prednisolone and antirheumatoid drugs such as D penicillamine altering the structure or physical properties of collagen also influence joint laxity[27] and generalized joint hypermobility is commonly seen in alcohol-dependents[109]. Generalized joint hypermobility can even occur as a secondary manifestation of inflammatory disorders such as rheumatoid arthritis (in which case the clinical picture can be complicated by a secondary neuropathy)[27] but also be exhibited during pregnancy, under the hormonal influence of oestrogens and relaxin notably[17,108].

Apart from HMS, generalized joint hypermobility is displayed in a variety of congenital disorders ; the alluded MFS, OI, EDS [3,29,31,51,57,58] or again stickler's syndrome[31,110], as connective tissue disorders, are all characterized to some extent by joint hypermobility; the latter is also seen in chromosomal disorders such as Down syndrome[58,111] or metabolic disorder such as homocystinuria and hyperlysinemia[58]. In the light of this multiplicity of possible aetiological factors, the determination of their relative contribution to one's demonstration of hypermobility appears nothing less than challenging. Yet, in 2004, investigating the genetic influence on joint hypermobility in a healthy population of female twins, Hakim, Cherkas and Grahame alleged that its heritability (percentage of the phenotype explained by genetic factors) was as high as 70%[23]. Commenting further on their results, they clarified their statement by adding that *"about three quarters of the influences on hypermobility are of familial origin"*[51].

Focussing on the symptomatic expression of joint hypermobility, the general opinion is that it runs though family, manifesting an autosomal dominant pattern of inheritance[7,23] (as stated for EDS-HT by the Villefranche nosology and Brighton criteria for the HMS), yet gender-influenced[1]. Members of the same family nevertheless may express varying degrees of laxity and may even be unaware of its presence[23]. Besides, HMS presents overlapping features with MFS, EDS and OI and is extensively reckoned as undistinguishable from EDS-HT[21]; given theses aforementioned characteristics and

in the view of its benign character, HMS is logically considered as a forme frustre, namely attenuated, of an HDCT[22].

Previously in this work, we have introduced a definition of the HDCTs in those terms : *"a group of phenotypically related inherited conditions caused by aberrations in genes encoding [the proteins of] the connective tissue matrix (collagen, elastins, fibrillins and tenascins)"*[28]. Yet for the layperson in histology, the denomination "connective tissues" can remain perplexing. Practically, it refers to one of the four basic tissues* of the body, derived from the mesenchyme and characterized by separated cells and abundant intercellular substance. Connective tissues in general are found throughout the body under many different forms and with diverse functions (from the connection of other tissues and support of organs to the repair following injury and metabolism) ; indeed, this type of biologic tissue include two broad categories :

- **the connective tissue proper**, also called general connective tissue (loose, dense, elastic, mucous, reticular, or adipose). The general connective tissue is made up of specialized cells (fibroblasts notably) immersed in an extracellular matrix, itself comprehending fibbers (collagen of various types, reticular fibbers, elastic fibbers and fibrous adhesive proteins) in a ground substance filling in between the fibbers and including glycosaminoglycans and proteoglycans. Type I collagen is predominate in general (but also in specialized) connective tissue and is overall abundant in tendons, ligaments, joint capsule, skin, demineralised bone and nerve receptors.
- **the specialized connective tissue** (blood and the cartilage and bones). The cartilage is made up of chondroblasts, chondrocytes and chondroclasts immersed in an extracellular matrix comprehending primarily collagens fibbers (type I predominanting in fibrocartilage and type II in hyaline cartilage) in a ground substance made up of glycosaminoglycans, proteoglycans and agrecans. The bone tissue is made up of osteoblasts, osteocytes and osteoclasts located at the periphery of an organic matrix with predominantly type I collagen (but also types III, notably found in extensible connective tissues such as the vascular system, skin and lungs, V, and X) with minimal proteoglycans and other proteins[34,112].

As explain Kadler and Wallis[113], speaking about the biomolecular basis of joint hypermobility, a delicate balance between stiffness and elasticity exists in connective tissues. While the former is provided by long collagen fibrils arranged in a special

* i.e. morphologically similar cells and associated intercellular matter

manner according to its location in the body, the latter depends on the placation of collagen fibbers and from elastic fibbers. Therefore any alteration in the encoding, synthesis, biochemical processing, structure or amount of any compound of the extracellular matrix (i.e. fibres and groups substance) can tilt the balance towards elasticity and lead to an infinity of disorders. Moreover, as a result of the complex interplay between extracellular matrix components, these disorders can either be phenotypically distinct, phenotypically similar or presenting with overlapping phenotypic features.

In contrast to other HDCTs, the underlying genetic defect in HMS/EDS-HT remains unknown[7,31]. Hypermobility could be an abnormality of type I collagen, but this remains to be proven.. Yet, an abnormal ratio of type III (thin and elastic compared to type I) to type I (characterized by a high tensile strength) collagen fibbers has been observed in some HMS patients and is therefore thought to be the cause of their decreased tissue stiffness[1]. Some studies suggested that TNXB (coding for tenascin, some glycoproteins of the extracellular matrix) mutations could be identified in about 5% of the EDS-HT patients[24,113]. A mutation of the COL3A1 gene for collagen type III in a single family considered affected by EDS-HT has been found. Yet this mutation has been shown to be typically present in the vascular type of EDS[22,7]. Thus, this conundrum appears nowhere near to be solved… but there still exists some research trails notably amongst the family of "small leucin-rich proteoglycans"(SLRP) which are known to interact directly with fibrillar collagens. Two SLRP, lumican and fibromodulin, have been found deficient in transgenic mice displaying severe joint hyperlaxity and age-dependant osteoarthritis, namely with a phenotype close to EDS-HT. The deficiency of other SLRP, namely decorin, dermatopontin and mimecan are also involved in EDS-like phenotypes with skin hyperextensibility and ultrastructural changes in collagen fibril diameters[7].

3.5.2 A possible involvement of the nervous system

The retrieved literature shows a feeble yet recently rising interest in the possible involvement of the nervous system as a causative factor in the pathological presentation of HMS. Concerns arouse _notably but not only_ with the increasing evidence of the association of HMS and anxiety disorders, but also with the observation of

cardiovascular regulations anomalies and the multiplicity of associated complaints in HMS sufferers. Despite the scarcity of the literature, it is possible to suspect an implication of the CNS as much on the somatic and vegetative system level as on the central nervous and peripheral nervous system level. Whether these anomalies are the result of the underlying HDCT or rather participate as a causative factor to the pathological presentation of HMS remains to be determined and further investigations are needed. However, we propose to review the ones that have been more or less commonly argued as possibly aetiological.

Starting with the peripheral nervous system, Grahame mentions in 2000 a surprising observation made by fellow researchers who found EDS-HT patients to be resistant to local anaesthetics (administered either by intradermal infiltrations or by topical application). They ascribed this anomaly to either the connective tissue or the nervous tissue itself. According to them, in the first case, modifications of conjunctive tissue could augment the clearance of the administered drugs in the environment of the nociceptors, in the second case there could be an increased sensitivity of the nociceptors or anomalies of the nociceptive message itself[19]. A similar observation was made in 2005 by different experimenters who noted that intradermal lidocaine injection had a much shorter effect in HMS sufferers[114]. Already in 1999, Russek was pondering the relative involvement of connective versus nervous tissue in the case of neurological system anomalies. Referring to the study of El-Shahaly and El-Sherif, she wondered whether the increased incidence of acroparesthesia (disturbed sensory perceptions in the limbs) reported in HMS sufferers "*may be due to abnormalities in the nerve tissue as well as surrouding connective tissues*"[1]. On the other hand, the proprioception acuity has been proven to be impaired in HMS patients[115]. Joint position sense and vibratory perception sense at the level of the knee joint were found to be significantly impaired in HMS population[115,116]. Alleged pathological mechanisms included damage to joint receptors, enhancement of the number of activated mechanireceptors in the joint, and negative effect of the pain on the proprioceptive acuity. Although only evidence in the knee, the latter is thought to be impaired all over the body.

The central and peripheral autonomic nervous system would also be subjected to disturbances of its function, i.e. dysautonomia. Investigating the occurrence of dysautonomic symptoms (e.g. fatigue, heat intolerance, palpitations, syncope…), Gazit et al. established that dysautonomia could be accounted for an extra-articular

manifestation of the HMS. They provided in this study pathophysiological basis for the incidence of these symptoms that gives autonomic system a good deal. Despite an intact vagal control of heart rate, HMS patients would present a compromised "functional" sympathetic reserve, an adrenoreceptor hypersensitivity (i.e. hyperresponsiveness of α1 and β1 adrenoreceptor caused partially by an increased responsiveness of the second messenger cAMP)[105].

Evidence of a an increased incidence of anxiety disorders and anxiety traits in the HMS populations could also support a possible dysfunction of the autonomic nervous system in the HMS population. This relatively recently alleged correlation between anxiety and hypermobility[97,98] could yet also be explained by an inadequate proprioception or again by the commonly occurring chronic pain in HMS[96,98]. The neurological aetiology in the exhibition of psychiatric symptoms in association with HMS has been further documented by Eccles et al. in a 2012 study[117]. Performing brain MRI on hypermobile individuals diagnosed thanks to the Beighton score, the observed structural differences in certain cerebral regions in comparison with other psychiatric populations. Cerebral regions involved in the emotion processing (amygdala, thought to mediate anxiety and psychosomatic conditions in HMS), were found to be of comparable or greater volume, while others involved in emotional arousal, negative emotions and attention (anterior cingulate cortex and parietal lobe) were found to be of lesser volume. As for the volume of the superior temporal lobe, it was found to be correlated negatively with the degree of hypermobility.

The possibility of a neurologic phenotype in HMS sufferers has finally been evoked by Voermans et al in 2009. Associated reduced sensation, muscle weakness (it is noteworthy here it to mention that hypotonia, as seen in Down syndrome for instance, plays an important role in hypermobility), with myotpathic changes would characterise HMS sufferers[91]. All the aforementioned studies appear to do their bit towards the recognition of the involvement of the nervous system in HMS. Yet the determination of the range of this involvement and of its causative versus reactive nature still needs to be determined.

3.5.3. Biomechanical and kinesiological basis: selected aspects and trails for the conservative management of the hypermobility syndrome

As we have previously demonstrated, hypermobility's predominant repercussions are found on the musculoskeletal or locomotor system, hence its primarily rheumatologic setting. The locomotor system has for main functions the production of movement (motricity) and the keeping of the posture (postural activity) of which the study pertains to the fields of biomechanics and kinesiology. Logically, it is in these domains that the aetiological basis of HMS appears the most concrete and that the most promising suggestions have been made in terms of practical management of the condition. We have already tackled both these branches of knowledge by introducing this chapter with a hint of arthrology, and by later developing the possible biomolecular and neurological basis of HMS. In this section we intend to further develop the mechanisms and extent of locomotor system's structural and functional impairment which is seen in HMS patients. In other words, we will unveil the structural defects of proprioceptors, muscles, tendons and capsuloligamenous elements and expose the ensuing functional disablement of the posture, gait and balance in people suffering of HMS.

3.5.3.1. Locomotor system's structural defects seen in hypermobility syndrome sufferers

As reminds us Beighton et all, the locomotor system's integrity and protection is highly dependent on the integrity of the afferent proprioceptive arcs and the resultant efferent control of the muscle tone[118]. Indeed, the proprioceptors, responsible for the position and movement sense, assist in the coordination of complex movement systems but also prevent undesired movements such as hyperextension and hyperflexion, and play a protective role in injuries[116]. In HMS patients however, the joint proprioception appears to be impaired, if not all over the body, at least at certain articulations. Rombaut et al.[115] demonstrated in 2010 that knee joint (more than shoulder joint) proprioception was reduced in EDS-HT patients, possibly because of damaged joint receptors, reduced joint receptor activation or impaired proprioceptive acuity as a result of widespread

pain. Ruling out a possible impairment of the vibratory perception sense in the knee and the shoulder, they claimed that the *"sensory impairment in proprioception is a result of deficits in joint receptors and muscle tendon receptors rather than cutaneous tactile receptors"*.

This hypothesis of proprioceptive impairment in HMS patients has had been previously tested and clinically validated by other researchers. Ferrell et al.[119], who also had previously demonstrated a diminished proprioceptive acuity in interphalangeal joints in HMS patients, showed in 2004 that a specific physiotherapy regimen could enhance proprioception in these patients. Using closed kinetic chain exercises to promote muscle cocontraction, and facilitate knee joint proprioceptors by increasing intraarticular pressure (stimulating Ruffini nerve endings) and static hamstrings exercises, they notably managed to improve the proprioceptive sensations and the balance board performance in their set of HMS patients. Similarly, Sahin et al.[116] showed in 2008 that a regimen of kinaesthesia exercises (walking with eyes closed, standing on one extremity…), plyometric exercises and balance exercises (biomechanical ankle platform board, board balance wood, minitrampolin) could enhance the decreased proprioception seen in HMS patients. It is unclear whether this proprioceptive deficit progressively develops in HMS patients or rather is present at birth. However, a common history of clumsiness and motor delay in childhood in these patients would support the second hypothesis[119].

According to Rombaut et al., when the proprioceptive acuity decreases, *"the functional stability can only be maintained if there is sufficient muscle strength for the decrease in acuity"*[115]. Indeed, as reminds us Beighton et al, "*the quality and nature of the muscle fibres contributes both in terms of their physical ability to stabilise the joint and in terms of their anatomical bulk, which might act to impeded joint movement by creating a large muscular mass"*[118]. However, Rombaut and co-authors have proved that the dynamic contribution to muscle and tendons (active system) in the functional joint stability is also impaired in HMS patients. In a 2012 study, Rombaut et al[120]. investigated the passive properties of the plantar flexor muscle-tendon tissues in EDS-HT patients and found that structural changes resulting in reduced muscle tension and tendon stiffness could be observed. In 2013, Investigating quadriceps muscle mass and function in EDS-HT patients, Rombaut[121] found that they presented with lower extremity muscle weakness (reduced muscle strength, reduced muscle strength

endurance and diminished functional performances) in the absence of muscle atrophy but with evidence of muscle imbalances. Voermans et al.[122], who had previously ascertain a global muscle weakness in EDS patients, correlated it with the fatigue severity, often encountered by these patients in a 2011 publication. In their 2009 publication, which has been discussed earlier, they had also put forward myopathic changes in the muscle tissue of various EDS types sufferers including the HT type[90]. Thus, if the muscle mass can at first sight appear within the physiological norms in HMS patients, the quality of the muscle tissue is altered, namely, its physical ability to stabilize the joint is decreased.

3.5.3.2. Functional impairment of the locomotor system in hypermobility syndrome sufferers

The posture is defined as a position in which an individual performs various activities (i.e. standing, walking…). It is controlled in a coordinated manner by the sensory system (vestibular, visual and proprioceptive systems), the central nervous system and the musculoskeletal system in order to cope with various destabilizing situations[105]. Now, we have established above that at least the proprioception and the musculoskeletal system (at the level of muscle tendon units) were altered, hence deficient in HMS sufferers. Logically a variety of studies in the last 10 years or so have showed that the postural activities and the function of the locomotor system was altered.

Investigating the static posture (i.e. standing) and joint pain of HMS sufferers with the help of the Reedco posture score and VAPS, Booshanam et al[106] found significant deviations with regards to a control group of non-HMS sufferers, particularly at the level of the head, hip, upper back, trunk and lower back. They correlated these postural defects to the possible multiplicity of abnormal structures in the spine and to the adaptation of the torso to secondary deviations exerted by the limbs. The joint pain (more important in the knees, wrist and lower back) was however not fully correlated to the postural deviations. Yet according to them, the posture in HMS sufferers is primarily affected by pain, which is the initiating factor for most of the postural deviations; it is also affected by changes in the musculoskeletal system, the increased susceptibility to unwanted joint stresses leading to acute soft tissues and hard tissues injuries, and joint instability. Along these lines, as a result of the impairment of a joint,

the others are affected as the body compensates for the injuries, compromise the posture as a whole.

The dynamic posture (i.e. gait) of HMS sufferers, have also been the object of studies; Galli et al. in 2011[123], Rombaut et al. in 2011[124] and Rigoldi et al. in 2012[111] found converging evidence towards a non-physiological gait pattern in these patients, with lower values of absorbed and generated work and where main limitations were present at the pelvis, distal joint and ankle joints. Possibly due to global muscle weakness and hypotonia, this impairment of the gait would also aim at compensating an increased ligamentous laxicity (at the level of the pelvis for instance). Celletti et al. in 2012[125], also correlated the fatigue severity to the abnormality of gait seen in EDS-HT patients and showed that the higher the fatigue, the less force generated and maintained by muscles during gait. In parallel, the function of the lower limbs in HMS sufferers appears to be less than in normal individuals. Using the lower extremity functional scale, which investigates tasks ability such as walking a mile, sitting for an hour or hopping, Celletti et al.[126] investigated in 2011 the impact of hypermobility on the lower limbs function. They found that the degree of disability in HMS patients was comparable to patients with osteoarthritis; moreover, this comparable level of impairment was arising 10 years earlier for HMS patients that for the ones with osteoarthritis. The degree of disability in HMS patients was also increasing with patient's age and overall perceived pain, but decreasing with Beighton score which supports the postulate along which musculoskeletal symptoms in HMS worsen with age and are often linked to progressive joint stiffness.

It remains unclear whether theses differences of static and dynamic postures are the direct result of micro trauma (to which HMS patients, because of the fragility of their connective tissues are more prone) or rather if these micro trauma negatively impact the postures, resulting in the discrepancies observed in HMS patients. According to Ferrell et al.[119], the degeneration of ligaments seen in HMS patients (caused by repetitive stress and strain and delayed healing) would contribute to functional impairment by causing proprioceptive loss: proprioceptive loss and so abnormal firing of mechanoreceptors would inhibit the dynamic stabilization process of cocontraction, leading to the adoption of biomechanically unsound positions, which could lead to microtrauma. Simmonds and Keer for their part, referring to Bergmark, argue that hypermobile individuals frequently overuse the global muscle system and have difficulty recruiting the local postural muscle system[127]. However, one cannot

completely disregard the almost certain interweaving of all these mechanisms and Booshanam et al.[106] for their part, settle for a vicious circle of abnormal stress and strain of the soft tissue, decreased stabilizing function, proprioceptive loss and typical deviations in the posture in HMS patients

3.6. Therapeutic strategies proposed for the management of the hypermoblity syndrome: physiotherapy, pharmacotherapy and others

The extent and variety of HMS's clinical manifestations logically suggests a multidisciplinary management of the condition[51]. Incidentally, the combination of different medical fields' approaches is invariably proposed in the most recent publications. However, most of the treatment strategies presented by their authors emanate from their clinical experience and have not been confirmed by evidence[3]. Besides, each patient presenting with a specific set of clinical manifestations and afflictions, the treatment plan is bound to be tailored to the needs and expectations of each HMS sufferer[51] and logically, general guidelines for managing HMS are still lacking[3]; even so, the actual trend is at the combination of medication, physiotherapy and fitness activities, possibly complemented by surgery, psychological management and other more or less anecdotal therapies[3,29,51]. As the general consensus is that physiotherapy represents the mainstay of the HMS management, treatment options pertaining to this domain will be first reviewed. Other therapies, notably pharmacotherapy and surgery will be also discussed as, as Rombaut et al. found, they are respectively extensively underwent by hypermobile patients[128].

3.6.1. Physiotherapy as the mainstay in hypermobility syndrome management

Once the diagnosis of HMS has been made, reassurance of the patient about his condition _regardless of the extent of the disablement it has caused_ is the first step. As Lawrence explains, many patients are worried about more serious diseases like rheumatoid arthritis or systemic lupus erythematosus[129]. Also, the set of possibly long-standing symptoms that HMS patients experience may have been source of

psychological distress and social issues[59]. Therefore, explaining their symptoms and outlining the fact that the syndrome is non-progressive and non-inflammatory allows alleviating considerable suffering[58,129].

In a second phase, and as for any other physiotherapeutic management, the one of HMS classically requires an initial examination (subjective and objective) to be performed; Keer and Butler emphasise the need for a thorough anamnesis (subjective examination) to be taken, notably in order to acknowledge the aggravating and alleviating activities/positions but also in order to obtain a full history of the patient's past and present disorders in all systems[59,104]. The objective examination, guided by the anamnesis and the observation, focuses on the analysis of the standing and dynamic postures, soft tissues mobility, joint mobility, muscle function and strength and pain assessment. Targeted neurological or orthopaedic tests can be needed[130] and proprioception can be tested, for instance with a Romberg test[104]. We will not come back here on the specific diagnostic means existing for HMS, neither on the typical physical features of hypermobile patients, as they have been respectively treated in 3.2 and 3.4. These key-point of the hypermobile patients' examination allow a tailoring of the goals and treatment strategies to their particular set of problems.

The multidisciplinary approaches adopted in the hypermobility clinics of London and Whipps Cross (United Kingdom) aim at treating the treatable presenting lesions, managing both the acute and chronic pain and encouraging self-help[29]. For Simmonds and Keer, it is important to develop a prioritized problem list with agreed short, intermediate and long-term goals, as, as they argue, it is the key to successful client care[59]. On a more physiotherapeutic standpoint, treatment strategies proposed by Edwards-Frowler and Keer*, include[28,104]:

- reassurance, education (avoiding resting in end-of range postures) and advice (rest, life-style modifications, judicious use of aids and support, exercise and fitness activities),
- developing core stability
- enhancing joint stability and improving joint proprioception
- restoring normal (hyper)mobility where it has been subsumed by stiffness
- reversing deconditioning, promoting general physical fitness and stamina by aerobic exercise

* two physiotherapists of these same hospitals

- pacing, coping, encouraging management and self-efficacy

A thorough review of the treatment options available for HMS sufferers is beyond the scope of this thesis, especially as the majority of them have not been evidenced in terms of efficiency. However, a complete description of the physiotherapeutic means and their possibilities of adaptations in the management of adult HMS patients can be found in [104]. According to Rombaut et al. muscle strength training, massage, stabilization training, electrotherapy, manual therapy and aquatic therapy are the most frequently proposed treatment options to HMS patients[128]. Simmonds and Keer emphasize that exercises should be performed in a pain-free manner at home or in consultation[59]. Stretching techniques to isolate tight muscles without stressing the surrounding joints may reduce symptoms by improving balance and control[58]. Mobilizations should always be gentle as it is thought to increase the degree of hypermobility of articulations (in any case, never more than 3 times a week)[129]. In the management of chronic states or in the intermediate stage of rehabilitation, the patient's education and lifestyle modifications are of primary importance Simmonds and Keer for instance recommend the use of mirrors or videotaping to promote the correction of deleterious postures and or movement[59]. Lifestyle modifications would also prove to be very rewarding in terms of prevention of further degradation of the patients' state and a rather complete list has been given by Castori (see table 9).

LIFESTYLE RECOMMENDATIONS AND SELF HELP
- promote regular aerobic fitness
- promote fitness support with strenghtning, gentle stretching, and propriception exercises
- promote postural and ergonomic hygiene, especially during sleep, at school and at workplace
- promote weight control (BMI<25)
- promote daily relaxation activities
- promote lubrication during sexual intercourse (women)
- promote early treatment of malocclusion
- avoid high impact sports/activities
- avoid low environmental temperatures
- avoid prolonged sitting positions and prolonged recumbency
- avoid sudden head-up postural change
- avoid excessive weight lifting/carrying
- avoid large meals (especially of refined carbonhydrates)
- avoid hard foods intake and excessive jaw movement (ice, gums…)
- avoid bladder irritant foods (e.g., coffe, and citrus products)
- avoid nicotine and alcohol intake

Table 9 - List of lifestyle recommendations and self-hep, reproduced from *Ehlers-Danlos syndrome, hypermobility type: an under-diagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestation* by Castori, 2012.

3.6.2. The restricted and sometimes counter-productive possibilities of pharmacotherapies

In a 2011 study about 79 adult EDS-HT sufferers, Rombaut et al found that 92,4% of them were using medication as monotherapies but also for a large majority in combination[128]. Pharmacotherapy (generally administered orally or by injection) in the case of HMS is directed primarily towards the management of pain[29,51]. Other non-negligible aims of medications include the control of local inflammatory processes and the diminution of generalized fatigue states and possible depressive states[128].

As mentioned earlier, pain is the predominant and unifying symptoms observed in HMS sufferers. Logically, its management is of first importance for these patients and analgesics (as a monotherapy or in combination) are the most commonly used drugs for this syndrome[3,128]. Ideally, their use should be restricted to these mild, moderate or severe pains which rest and lifestyle modifications do not sufficiently alleviate (as it is often the case)[58]. Acute pain is generally managed effectively with the use of analgesics: mild pain is generally treated with NSAIDs (ibuprofen, paracetamol, naproxen)[3,51], moderate pain by weak opioid drugs (such as tramadol and codein)[3,51] and severe pain _exceptionally and only if these aforementioned drugs have failed_ with potent opioids (oxycodone, buprenorphine) [51]. In the case of chronic pain, because of a possible defect in pain processing, the use of analgesics and NSAIDs remains ineffective[51] ; pain modulator drugs such as tricyclic antidepressant and SRI can then be proposed to the patient[3].

Local inflammatory processes, characteristic of soft tissue lesions (for instance overuse syndromes) which are often seen in HMS sufferers can be treated with local steroid injections. However, the use of steroid soluble preparations is preferable to depot preparations, their injection should be administered at minimal dose and perfectly targeted[51]. Chronic fatigue, which is thought to be primarily caused by cardiovascular dysautonomia can be treated by corticosteroids (fludrocortisone), ultimately by vasoconstrictors (midodrine) if life-style recommendations prove to be insufficient[3].

It has to be noticed that pharmacotherapy, even for mild to moderate pain, should be considered extremely carefully by the practitioner. Indeed, the adverse effects of some medications in HMS are exacerbated, rendering their use counter-productive.

For instance, acetylsalicylic acid therapy for the pain management for HMS sufferers is classically ruled out, notably because of its antiplatelet action which increases the tendency to haemorrhages and ecchymoses[3]. NSAIDs, because of their risk of gastro-intestinal bleeding should be used sparingly[51] and some authors consider their use neither practical nor effective[1]. Myorelaxant, commonly used for isolated muscle contractures may cause the amplification of joint instability, multiple dislocations and consequent exacerbation of pain and fatigue[3]. Lastly, because steroids inhibit the collagen synthesis by fibroblasts, their use will have an adverse effect on the tensile strength of already intrinsically collagen rich yet weakened tissues[29,51].

3.6.3. Surgery and other approaches

The 2011 study published by Rombaut et al.[128] revealed that in a large proportion of EDS-HT sufferers (70,9%), single or multiple surgeries had been performed mostly for the lower (33 patients) and upper limb (21 patients). However, the effect of the surgical intervention were considered favourable for only 33,9% of the patients. Negative outcomes of surgical managements could be explained by several factors: the friability of tissues, possible difficulties of homeostatis due to the fragility of vessels, a delayed and/or incomplete healing, a thin and unsightly scarring and problems in wound healing closure with suture tearing and wound dehiscence[51]. Before these disappointing results, it is considered preferable to postpone surgical approaches and favour conservative ones[3]. Going back to the study of Rombaut et al. but on a different note, it is interesting to notice that a total of 52 surgeries had been performed amongst the 21 EDS-HT patient who had underwent upper limb surgeries[128]. This can confirm the high susceptibility of hypermobile patient to present various and recurrent musculoskeletal afflictions but also can suggest a high rate of unsuccessful and corrected surgeries.

Other therapeutic approaches than physiotherapy, pharmacotherapy and surgery can be proposed to HMS sufferers; podiatry can be envisaged as many hypermobile patients present bilateral pes planovalgus. Occupational therapy can help hypermobile patients in task performing enhancement[51]. Lastly, cognitive behavioural therapies, because of the positive outcomes they have shown in terms of quality of life improvement, pain and depressive states management, and self confidence enhancement, can be recommended for most severe cases[19].

3.7. Outcomes of treatment and prognosis

Probably because of the reputed benignity of the syndrome, argued prognoses for the disorder differ according to authors. Maybe rather optimistically, Simpson argues that because of the non progressive nature of the syndrome, the prognosis of the patients with HMS is good[58]. Yet this very same authors writes a few lines later that the potential complications of the syndrome *"underscore the importance of making an early diagnosis and educating the patient"*. For Russek, the prognosis is mixed. As she argues, "*there is no cure for the disorder. The goal for treatment therefore is no return to normal (ie. not hypermobile) joint mobility but restoration of relatively pain-free function"*[56].. Castori finally outlines the possible negative factors influencing the prognosis, notably the chronicisation of pain and the resistance to treatment[3]. In our opinion, positive factors influencing the prognosis would be the establishment of a correct diagnosis as early as possible and its management by trained physiotherapists.

4. Nerve entrapments syndromes, the example of the thoracic outlet syndrome

After having thoroughly described HMS and demonstrated its pervasive, yet nebulous and often overlooked nature, let us address our topic of interest from the opposite angle: the one of NES. As it has already been observed, a vast collection of nerve entrapment syndromes has been defined, as up to that date we tally about fifty different ones. NES are named according to the compressed nerve, the anatomical area or tunnel in which occurs the compression, the motion producing the compression or the name of the describing authors. They can affect any limb, or even the trunk and are more or less prevalent amongst populations[6]. But they also all can be characterized by the same aetiological and clinical definition, namely the *"lesions of individual peripheral nerves resulting from injury at vulnerable anatomical sites"*[5]. However and rather ironically this very mechanism of injury occasionally remains ignored or unknown. Yet, up to that point of this thesis, we have established generalized hypermobility as a precipitating factor in the onset of seven different NES, including the TOS. Because of their multifarious clinical presentations, an extensive review of each of these seven NES appears impracticable and unachievable. We therefore chose to focus our attention on the one that was the inspiration for this thesis and which incidentally has been correlated with HMS: the TOS. Its presentation will follow as slightly different course than the one which has been chosen for HMS in order to make the description of this condition clearer. In this section, we will first provide the reader with basics of neurology, expose the pathological mechanisms at work in NES and generally attempt to accurately describe the TOS.

4.1. Introduction: from the peripheral nervous system to the nerve entrapment syndromes

Because of the nervous system's anatomical construction and ordained functional distribution, any structural impairment gives rise to a characteristic set of signs and symptoms. For instance, spinal nerve lesions show a myotomal and/or dermatomal distribution whilst peripheral nerve lesions show a peripheral nerve distribution ; thus NES all appear roughly with the same features, but distributed

differently according to the site of the entrapment. An acquaintance with these recurring patterns allows one to trace back to the responsible dysfunctional component of the nervous system. Therefore we propose to first get back to basics of neuroanatomy, especially regarding the peripheral nervous system as a whole; lastly, we will distinguish the NES from the other afflictions of the peripheral nerves.

4.1.1. General points on the peripheral nervous system[131-134]

The nervous system is structurally divided in two parts : the central nervous system (CNS) and the peripheral nervous system (PNS) ; the later is additionally subdivided into a somatic nervous system (SNS) and an automatic nervous system (ANS). The CNS comprehends the brain, protected by the skull and the spinal cord, protected by the vertebral column, while the PNS is made up with the spinal nerve roots, the spinal ganglions, the spinal nerves, the peripheral nerves and their endings, as well as a major portion of the ANS. The first two cranial nerves (olfactory and optic nerves) belong to the CNS, but the remainder is considered as a part of the PNS. However, for the better clarity of this review and unless specified otherwise, the term peripheral nerve will refer to the nerve plexuses and trunks issued from the spinal nerves. This simplification _on which agree a number of authors dealing with the afflictions of the PNS in general_ mostly pertains to a clinical and pathological standpoint: the testing of the cranial nerve's integrity is the object of a distinctive neurologic examination and their afflictions often conform to unalike aetiologies and/or mechanisms. Besides, the SNS processes sensory information (afferent fibres) and controls all voluntary muscular system (efferent fibres) within the body, whereas the ANS acts below the level of consciousness to control and regulate visceral functions through afferent and efferent fibres (organs, vessel, exocrine and endocrine glands).

The nervous system is furthermore characterised by its unique cellular organisation in which its functional unit, the neurone, is in charge with the transmission of the nerves impulses while the glial cells serves as support, nutritional, an protecting cells for the neurons. The neurons are indeed particularly remarkable for their excitability (ability to respond to a stimuli) and conductivity (ability to transfer a signal). Although the morphology of various types of neurones differs in some respect, they all can be characterised buy four distinct regions as exposed in the table 10

TYPICAL ORGANISATION OF THE NEURONES	
PORTION	DISTINCTIVE FEATURES
Cell body / soma / pericaryon	- unique portion of the cell surrounding the nucleus - responsible for the synthesis and the processing of proteins, and the reception of informations; - contains notably free ribosomes, smooth endoplasmatic reticulum, mitochondria, Golgi apparatus and characteristic structures called Nissl bodies (rough endoplasmatic reticulum
Dendrites	- numerous structures arousing from the pericaryon - in charge with the reception of the information - their disposition with regards to the soma differentiate three types of neurons (multipolar, bipolar or unipolar)
Axon	- unique structure of the neurone allowing the transmission of the information and ; starting from the axon hillock and finishing at the telodendrion (terminal arborisation of the axon) - filled with parallel arrays of microtubules and microfilaments which provide a structural stability and convey different materials - can be either myelinated or unmyelinated : in the first case a chain of Schwann cells* envelop a single axon (of bigger diameter) in a myelin sheath which provides an electrical insulation to the nerve (the myelin sheath is punctuated by special spaces called nodes of Ranvier allowing a salutatory (and thus faster) conduction of the electrical signals) ; in the second case, a chain of Schwann cells surrounds several axons (of lesser diameter) to insulate them. NB: Schwann cells are also a source of proinflammatory cytokines that participate in the inflammatory response exhibited by injured neural tissue
Synaptic button	- terminal structure of the axon, in which chemical synapses contain neurotransmitter vesicles released under the action of action potentials - synapses are connected either to muscles (motor end plates, glands or other nerve cells.

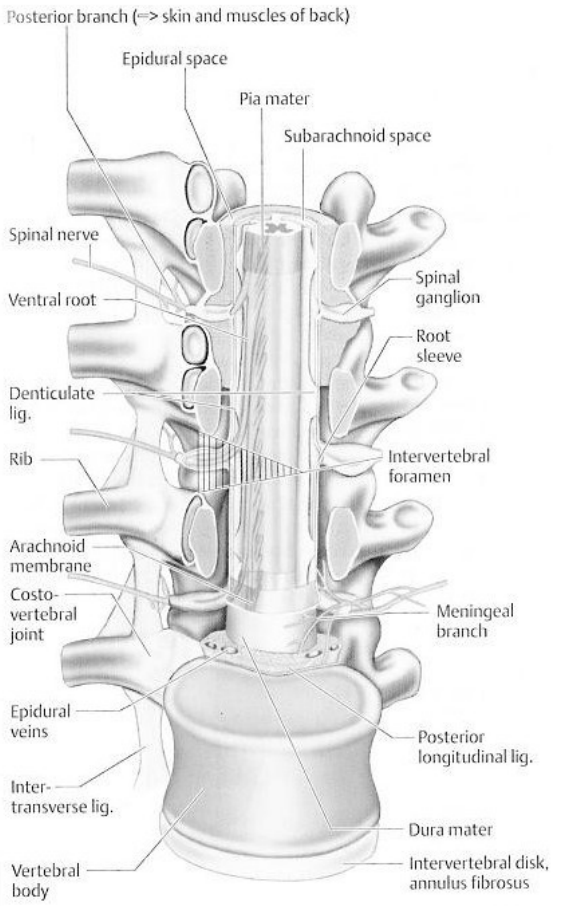
Table 10 - The four characteristic regions of the neurones

Inside of the spinal canal (namely the tube formed by the vertebral foramina of the piled up vertebral bodies), root filaments exit form the spinal cord ventrally and dorsally to form the anterior and posterior nerve roots. According to the law of Bell and Magendie, the anterior root carries only motor fibres (i.e. afferent from the spinal cord) which cells of origin lie in the anterior horn of the spinal cord, while the dorsal root carries only sensory fibres (i.e. efferent, to the spinal cord), which cell bodies are located outside the spinal cord in a swelling on the posterior root called posterior root ganglion. Anterior and posterior nerve roots pass at the level of the intervertebral foramen where they unite to form a spinal nerve, which is thus made up of both motor and sensory fibres. The spinal nerves are then named according to the regions of the vertebral column from which they emerge and we distinguish 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coxyggeal spinal nerve. After emerging from the intervertebral foramen, the constituting group of axons of the spinal nerve splits into recurrent meningeal branch, and then a posterior ramus and an anterior ramus. The recurrent meningeal branch re-enters the vertebral canal to innervate the meninges, namely the

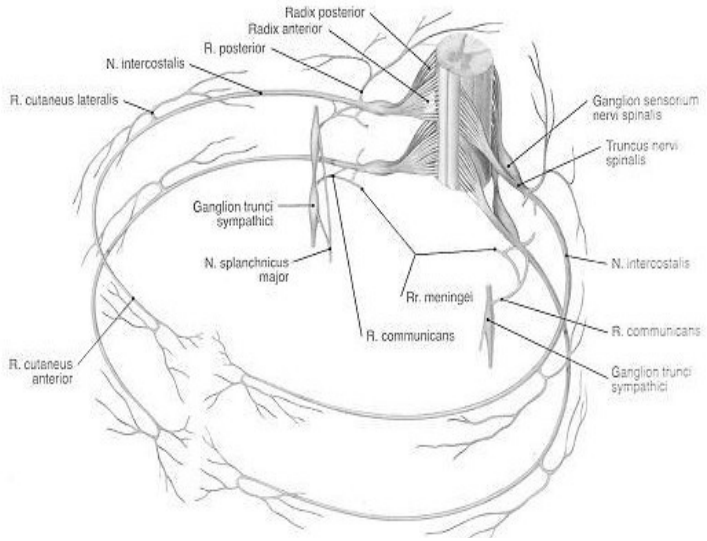
* the myelin sheath is produced by Schwann cells in the PNS but by oligodendrocytes in the CNS

protective membranes enveloping the CNS. The posterior rami innervate the paravertebral muscles, posterior parts of the vertebrae and overlying cutaneous area. The anterior rami innervate the skeletal, muscular, and cutaneous area of the limbs and the anterior and lateral parts of the trunk; in its initial part, it is also connected to the sympathetic ganglion by grey and white rami communicantes.

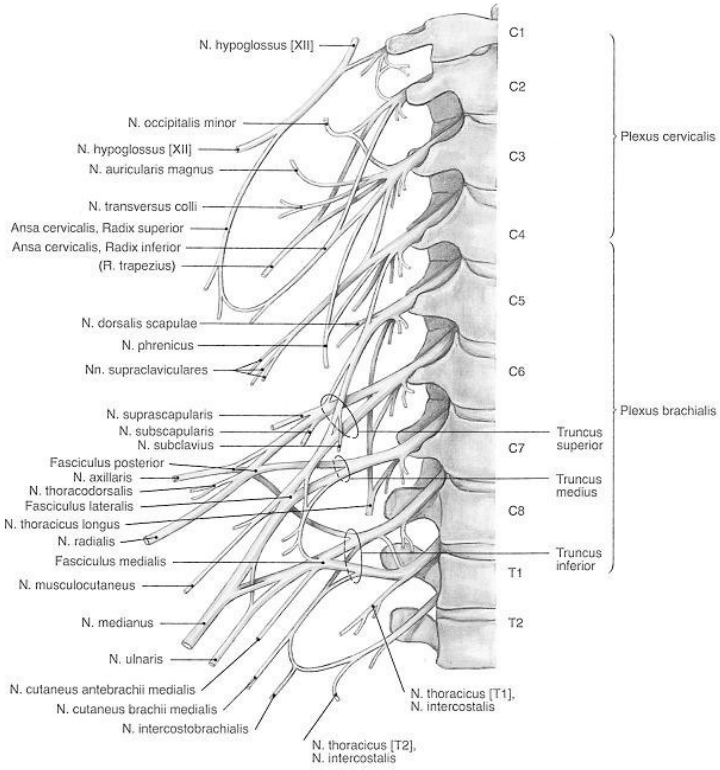
A



B



C



Picture 11 - The peripheral nervous system, selected aspects : exit of the spinal nerve roots from the spinal cord and junction into spinal nerve through the intervertebral foramina, example of the thoracic level in anterior view (A), scheme of two thoracic spinal nerves (B), overview of the cerviocal and brachial plexuses (C) reproduced from *Color atlas of Neurology* by Rohkamm, 2004 and *Sobotta Altlas of Human Anatomy Volume 1* by Putz and Pabst, 2006

At the exception of the thoracic nerves from T2 to T11, the anterior rami of all the spinal nerves join together and/or branch to form a network of nerves known as

nerve plexuses. The formation of nerve plexuses allows individual nerve fibres to pass from one peripheral nerve to another and this permits a redistribution of nerves fibres within different peripheral nerves. We distinguish three major nerve plexuses :

- the cervical plexus: arising from the anterior rami of C1 to C4 spinal nerves and lying deep to the sternocleidomastoid muscle, it provides cutaneous sensory information from the posterior scalp to the clavicle and innervates the anterior neck muscles and the diaphragm.
- the brachial plexus: arising from the anterior rami of the C5 to T1 spinal nerves, and proceeding through the neck, passing under the clavicle to the axilla and into the arm, it provides sensory and motor innervation to the upper arm, forearm and the hand ; although it appears tangled it is highly organize and predictable with little variation between people (its anatomy will be further developed in the section 4.2.1.).
- the lumbosacral plexus: made up roughly of L1 to S5 spinal nerves, and often with a small contribution form T12, the lumbosacral plexus in fact comprehends two portions : the lumbar plexus which supplies mostly muscles of the thigh and the sacral plexus which supplies mostly the muscles of the leg and foot.

The nerve plexuses distally give rise to nerves trunks and branches innervating the limbs or the head. The individual peripheral nerves trunks and branches bear an anatomically invariant relationship to the muscles and cutaneous zones that they innervate.

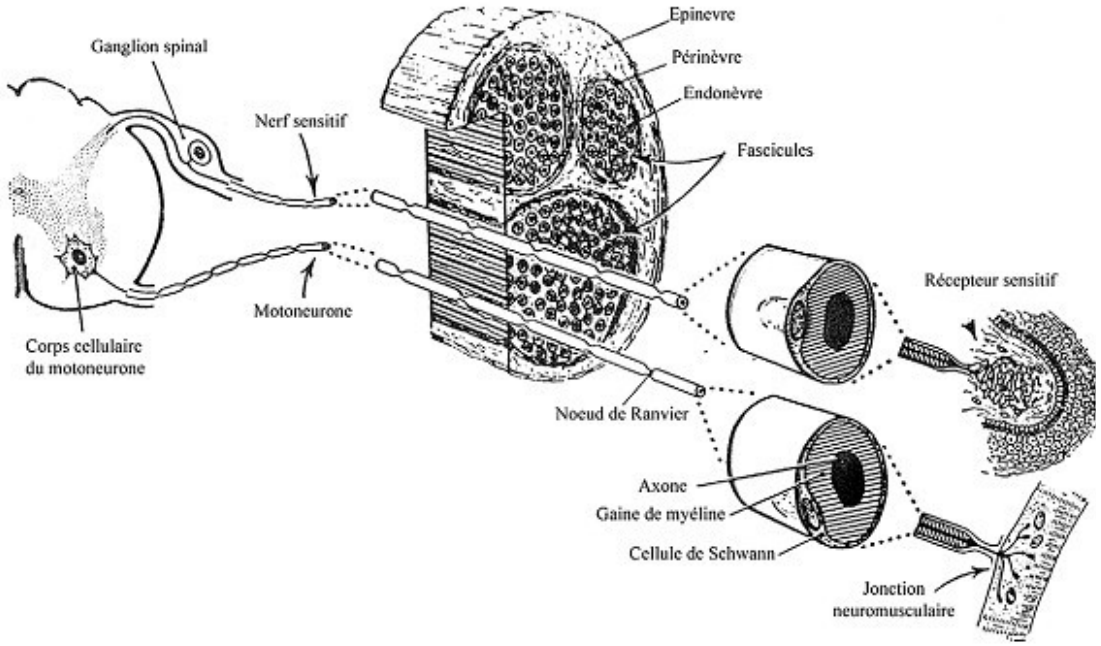
4.1.2. Structural anatomy of the peripheral nerves[135,136,137]

We have earlier chosen to restrict the term peripheral nerves to the nerve plexuses formed by the junction of regrouping fibres of the anterior rami derived from the spinal nerve roots, as well as to the more distally lying peripheral nerve trunks and branches[d]. Whilst the nerves plexuses always contain mixed fibres types (sensory, motor and autonomic, especially sympathetic), the peripheral nerves trunks nearly always do so. Structurally, the peripheral nerves can be defined as composite structures of nerves fibres, blood vessels and connective tissue support and capsule; the multiple axons or nerve fibres constituting the nerve plexuses or trunks are indeed organised in parallel bundles surrounded by different connective tissue sheaths which are in continuity with each other: the endoneurium, perineurium, and epineurium.

- the endoneurium defines a loose and delicate connective tissue sheath made up of a fine network of 30 to 50nm thick collagen fibrils; the latter are scattered in the longitudinal direction of the nerve fibres and provide a scaffolding through which capillaries network course to supply blood to nerve fibres and associated supporting cells. The endoneural space comprehends flattened fibroblasts, a homogenous basic substance, capillary vessels, macrophages which bath in an interstitial fluid milieu. The endoneurium becomes specialized to form an endoneural tubule around each myelinated axon or group of unmyelinated axons; the aggregation of single myelinated axons, groups of unmyelinated axons, their supporting structures and endoneurium defines so-called fascicles which are delimitated by a second layer of connective tissue, the perineurium.
- the perineurium defines a smooth and thin multilayered coat made up of collagen and to a lesser extent elastin arranging the fascicles by bundles; it is made up of a 6 to 15 layers of concentric connective tissue depending on the fascicular diameter. Its thick (40 to 80nm) collagen fibrils are tightly twisted and typically arranged in a different orientation (primarily longitudinal and then with a slightly changing inclination between the successive layers), conferring to the perineurium a laminated architecture. Densely packed fibroblasts, also called perineurial cells are connected with each other cell to cell to form a protective blood-nerve barrier. The perineurial space also contains a few fibroblasts and macrophages.
- the epineurium defines the stronger of the connective tissues protecting the nerve trunks ; it is made up of thick collagen fibres (60 to 100nm) oriented mainly longitudinally and sometimes also slightly obliquely along the entire length of the nerve trunk, but also of elastic fibres and fatty tissue. Fibroblasts, fat cells and a few red blood cells can be found between the collagen fibres. The epineurium binds perineurial bundles together with a looser connective tissue called the internal epineurium, while the external epineurium, wrapped around the internal epineurium separates the nerve trunk from the neighbouring structures. This outermost layer of supporting structure for the peripheral nerve emerges in the dura matter of the spinal roots.

As broached above, the peripheral nerve plexuses and trunks dispose of a vascular and nervous supply respectively called the vasa nervosum and the nervi nervosum. The vasa nervosum refers to small arteries derived from the large arteries travelling along the peripheral nerves and which provide blood supply to them. The

vasa nervosum enter the epineurium where it branches into arterioles and continues to ramify in various direction; it then pierces the perineurium where it forms capillary anastomoses in the fascicles. The nervi nervosum is composed of sensory and sympathetic nerves fibres which originate from the actual nerve fibres and the perivascular plexus. They are found in the epineurium, perineurium and endoneurium and thus, the connective tissue of the peripheral nerve is highly innervated. It is interesting to notice that the nervi nervosum possess nociceptive capabilities and contain neuropetptides that mediate the inflammatory response exhibited by nerve trunks exposed to irritating mechanical or chemical stimuli[137]. On another pathological standpoint, it is also interesting to notice that the nervi nervosum is itself innervated by thin plexuses of vegetative fibres, causing vasomotor troubles when they are injured; these vegetative fibres are of unequal distribution in nerves trunks, which accounts for the diversity of the symptoms linked to NESs (for instance, vasomotor troubles, notably oedema and hypersudation are more frequently observed in CTS because of the important number of vegetative fibres in the median nerve). [138]



Picture 12 - Structure of the peripheral nerve, reproduced from *Physiopathogénie des syndromes canalaires*, By Blancher and Kubis, 2007.

4.1.3. Functional anatomy of the peripheral nerves[137,139,140,]

Between 50% and 90% of the entire cell substance of the peripheral nerves consists of connective tissue[135] and accordingly, the connective tissues play a crucial role in the physiology and function of the peripheral nerves ; they first support the vascularisation, metabolism and nutrition of the nerves and after an injury, they promote scar tissue formation and the regeneration of the axons. But the aforementioned layers of connective tissue also allow the nerves fibres within a peripheral nerve trunk or plexus to derive considerable mechanical strength and to accommodate to length changes during movement.

The endoneurium provides an optimal mechanical and biochemical environment for the components of the fascicles, by maintaining the endoneurial space and fluid pressure so that its variation have no effect on the conduction of impulses on the axonoplasm. By its network of collagen fibrils, it arranges axons in an undulated way; when a nerve trunk lengthens these undulation straighten effectively lengthening axons with minimal to no increase in endoneurial pressure. Conversely, shortening of a nerve trunk causes the undulations to increase, enabling axons to adapt without being unduly compressed*. The endoneurium thus provides a resistance to tensile force.

The perineurium, because of its laminated architecture, acts as a viscoelastic tube, adapting by changing dimensions and thus maintaining a within the physiological norm pressure in the fascicles regardless of the length of the nerve and also resisting to tensile forces. Moreover, just as axons follow an undulating path within the endoneurial space, each fascicle takes a tortuous course within the nerve trunk. Fascicles repeatedly unite and divide long the length of the nerve to create fascicular plexuses. These plexuses enable the nerve trunk to adapt to changes in length, but also permit gliding between fascicles as nerves are twisted, compression or lengthened during joint movement. As mentioned earlier, the perineurium also serves as a blood-nerve barrier: the innermost connective tissue lamellae of the perineurium creates a metabolically active diffusion barrier, acting bidirectionally and that permits only certain chemicals

* it is interesting to notice that the protective role of the endoneurium is further proved by the pathology: the paucity of endoneurial collagen at the roots as compared with the nerve trunk indeed has been put forward to explain why some diseases processes selectively involve the nerve roots. The latter, which globally possess much less connective tissue and in which and individual nerve fibres with the roots are straight show an increased level of vulnerability.

and ions to come in contact with the neural tissue. For example, chemicals associated with oedema around a fascicle or infection around a nerve trunk do no come in contact with the intrafascicular environment keeping certain substances out of the intrafascicular environment. Because of its bidirectional functioning, if mechanical or chemical stimuli cause endoneurial inflammation followed by intrafascicular oedema, the resultant increase in endoneurial fluid pressure persists because the perineurium does not allow the inflammatory exudates to escape.

Because the epineurium is a loose, lipid rich layer of connective tissue, reinforced by transversely and longitudinally oriented collagen fibres it provides a protective cushion against compression (for instance, the sciatic nerve in the buttock region contains more fat than any other nerve). Moreover, the internal epineurium allows movement between the perineurial bundles and their relative gliding and this arrangement protects the nerve against compressive forces. This ability to adjust to movement is in addition most important with nerves than bend at an acute angle. It seems that nerves that have more fascicular and perineurial bundles can withstand compression more efficiently than those with just a few. The portion of epineurium of the individual nerves varies it supports the perineurial bundles with a looser connective tissue called the internal epineurium. This allows movement between the perineurial bundles, within the external epineurium. This arrangement will protect the nerve against compressive forces and because of this ability at sheltering nerves fibres of mechanical loads, fascicular plexuses and internal epineurial tissues are well developed in portions of nerve trunks susceptible to injury; for instance where nerve cross joints or pass through osseous (e.g. intervertebral foramen), osteoligamenous (e.g. carpal tunnel) or fibrous (e.g. arcad of Frohse).

Unlike the intestines, the nerve trunks do not possess a mesentery that attaches them to their surroundings ; however, they are fixed to adjacent connective tissue, sometimes called the mesoneurium at a few points at which they are especially vulnerable to mechanical damage. The mesoneurium allows a degree of slide and lateral movement against muscular and bony structures. Indeed, during limb movements, peripheral nerves exhibit a significant amount of sliding relative to surrounding tissues, which is facilitated by this mesoneurium. However, if the mesoneurium becomes fibrotic, it can shrink and adhere to the external epineurium or adjacent non-neural structures, thereby impairing mobility of the nerve trunk. It is interesting to notice that

larger nerve trunks are often found together with arteries and veins in so called neurovascular bundles surrounded by a common connective tissue sheath. These bundles form an anatomical unit that is clearly demarcated from the surrounded structures.

The aforementioned organisation and properties of the connective tissue permits to the nervous system to sustain the mechanical forces to which is it is submitted during movement. The concept of neurodynamics, as introduced by Shacklock reprises functional and structural neuroanatomical basis and explains how, as the nervous system participates to the generation of movement, it also accompanies it and reacts accordingly. Surrounding interfacing musculoskeletal structures, changing in dimension during the production of movement, indeed exert mechanical forces on the nervous structures. In reaction to these changes the nervous tissue gradually adapts with a combination of strain (i.e change in length), excursion (i.e sliding) and tensile stress (i.e. increase in intraneural pressure). As mentioned above, the strain or intrinsic lengthening of peripheral nerves is permitted by the unfolding of the undulations of nerve fibres and fascicles within their protective connective tissue sheaths. Once the neural tissues have unfolded to the point where their undulations are eliminated, they respond to their continued lengthening by sliding or excursion. The latter occurs either along the longitudinal axis of the nerve trunk or transversally and is facilitated by the surrounding mesoneurium. Finally, when sliding mechanisms have been exhausted, additional lengthening in neural tissues is associated with a diminution of the nerve diameter and an increase in intraneural pressure in the nerve trunk or tensile stress. The resistance to this tensile stress is, as mentioned above, owed to the viscoelastic properties of the connective tissue sheaths, which convert it into a modest compressive force. However, when this resistance to compression is overstepped, the nerve function is altered in a direct dose-response relationship and external pressure as low as 20 to 40mmHg can impair axonoplasmic transport, blood flow and nerve conduction. These level of compression occur during daily activities, but as long as the magnitude and duration is not excessive, their effects on neural structures are cmompletely reversible. It furthermore is interesting to notice that these reactions affect the nervous tissue in its globality, as the latter forms a continuum throughout the body. Yet they also occur in a non-uniform manner : the intrinsic characteristics of the different portions of the nerves (differences in fascicular plexuses and connective tissue content along a nerve) but also

the diverging kinematics of the joints crossed by the nerves, degrees of limitations in excursions at nerve attachment sites and degrees of exposure to different interfacing structures (bones, tendons…) differently affect the mechanical reactions of the neural tissue to movement.

4.1.4. Pathology of the peripheral nerves : focal neuropathies, multiple neuropathies and polyneuropathies

Afflictions of the PNS all present the same pattern, namely flaccid weakness, sensory deficits and autonomic disturbances. However, they show variable distributions and combinations depending on the localisation and extent of the lesion but also according to the underlying pathological mechanism[133]. The most common classification focuses on the localisation of the lesion and distinguishes those occurring at one or more spinal nerve roots (so-called radiculopathies) or occurring at one or more nerve plexuses/individual nerve trunks or branches (so-called peripheral neuropathies)[133,141]. As notice Bouche et al.[142], it is usual to omit in this classification the PNS conditions primarily involving the neuron cell body regions[*]). Besides the origin of the lesion, the distinction between radiculopathies and peripheral neuropathies stems from their slightly different range of possible pathomechanical processes (shortly introduced in the previous section of this work) but also from their distinctive symptoms presentations. Spinal nerve roots' afflictions indeed are characterised by a sensory and motor impairment respectively distributed along a dermatomal and myotomal arrangement. Lesions of peripheral nerve trunks, branches or nerve plexus on the other hand, are characterised by the impairment of the motor/sensory/autonomic territory(ies) which they innervate[132,143]. As afflictions of the peripheral nerves, NES are all characterized by the aforementioned symptoms; yet they are further distinguishable from many other types and subtypes of peripheral neuropathies, for they, by definition, affect a single nerve and commonly result of a compression injury. As this distinction presents an undeniable diagnostic and etiologic interest (see 4.4.), we propose to briefly introduce the common classification which is done of peripheral neuropathies.

[*] the so-called neuronopathies or ganglionopathies, which histopathologic changes are therefore found in the posterior root ganglion or in the anterior horn of the spinal cord

Peripheral neuropathies are categorised according to the extent of the lesion, namely the involvement of one or several nerves and according to its symmetric and length dependent fashion[144]. We thus distinguish three main types of peripheral neuropathies which are :

- the mononeuropathies: also called focal neuropathies, they are characterized by the involvement of a single nerve branch, trunk or plexus (plexopathy). They are most often of mechanical origin (trauma, prolonged compression…)[133] and can affect the peripheral cranial or spinal nerves. NES are classified under the latter category.
- the multiple neuropathies: also called multifocal neuropathies, they are characterized by the asymmetrical involvement of two or more isolated nerve branches, plexus or trunks (namely by the onset of two or more mononeuropathies) usually in close temporal evolution and sometimes simultaneously[144]. The symptoms (predominantly motor deficits) arise generally suddenly then decline (by spurts). They are the most often the result of ischemia (as seen in diabetes mellitus, although it most commonly causes polyneuropathy), infiltration (by bacteria as seen in leprosy).

Mononeuropathies:
- entrapment neuropathies - trauma - every cause listed under multiple neuropathies (below) may start with single nerve involvement
Multiple neuropathies:
- nervous vascularitis (HIV, polyarteritis nodosa, systemic diseases) - diabetes mellitus (mononeuropathies and lumbosacral radiculopathies) - sarcoidosis - leprosy - mutlifocal motor neuropathy (generally with persisting conduction) - Tangier's disease - initial focal types or multifocal types of polyradiculopathies (Lewis summer syndrome) - hereditary neuropathies caused by pressure hypersensibility
(Symmetrical) polyneuropathies:
- inflammatory or autoimmune polyneuropathies : *- Guillain-Barré syndrome and related* *- polyradiculoneuritis and related* *- neuropathies caused by vascularitis (extensive multineuritis)* *- sarcoid neuropathies* *- systemic/ connective tissue disease-related neuropathies (for instance in lupus erythematosus* - inherited polyneuropathies *- hereditary motor sensory neuropathies* *- giant axonal neuropathy* *- hereditary sensory and autonomic neuropathies* *- peroxisomal disorders (Tangier disease, abetalipoproteinemia)* *- lyzozomal enzyme deficiency.* - polyneuropathies caused by vitamin deficiency : *- thiamine, B1, B6* *- B12, folates* - polyneuropathies associated with cancer : *- paraneoplasic neuropathies (remote effects of cancer)* *- neuropathies caused by direct tumour infiltration* - polyneuropathies due to a metabolic disorder : *- diabetes mellitus* *- uraemia* *- hepatic cirrhosis* *- gout* *- hypothyroidism*

Table 11 - General causes of peripheral neuropathies and PNS disorders modified from *Neuropathies périphériques, polyneuropathies et mononeuropathies*, by Bouche et al, 2006

- the polyneuropathies: also called peripheral neuritis, they define a generalized, widespread process impairing multiple cranial or spinal peripheral nerves, usually in a more or less symmetric fashion. The disorder settles in a progressive fashion (weeks, months or years) with evolving symptoms which are most often sensory but can also be sensori-motor, motor or autonomic[141]. Polyneuropathies show a length-dependent symptomatology, namely the longest fibres are the first affected, hence their primarily distal distribution. In contrast with mononeuropathies, most polyneuropathies are of metabolic, toxic, infectious, inflammatory or paraneoplastic origin[143].

(Symmetrical) polyneuropathies (continued):
- polyneuropathy due to dys or paraproteinemia
- polyneuropathy due to infectious disease
- leprosy
- mumps
- mononucleosis
- typhoid and paratyphoid fever
- typhus
- HIV infection
- diphtheria
- botulism
- borreliosis, lyme disease
- polyneuropathy due to exogenous toxic substances:
- ethanol
- lead
- arsenic
- thallium
- triaryl phosphate
- solvents (e.g. carbon disulfide)
- drug toxicity (isoniazid, thalidomide, nitrofurantoin, disulfiram)
- neuroapathies associated with organ system failure:
- kidney, lung liver
- critical illness polyneuroapthy
- neuropathies associated with organ transplantation

Table 11 (Continued) - General causes of peripheral neuropathies and PNS disorders modified from *Neuropathies périphériques, polyneuropathies et mononeuropathies*, by Bouche et al, 2006

Amongst these three categories, peripheral neuropathies are also distinguished according to their aetiology. For instance, if a mononeuropathy can be caused by a trauma, it can also be the result of a metabolic disorder such as diabetes mellitus. However, the latter rather evolves into a polyneuropathy sensory impairement with a stocking/glove distribution. For information purposes, the most common causes of peripheral neuropathies and PNS disorders are presented in the table 11[145].

4.1.5. Close-up on a group of focal neuropathies, the nerve entrapment syndromes and the difficult characterisation of this concept

We have earlier introduced the concept of NES using the words of Fisher who described them in the simplest fashion as : "*lesions of individual peripheral nerves*

resulting from injury at vulnerable anatomical sites"[5]. This broad but unarguable definition*, is generally reprised under synonymous wordings by authors of the retrieved literature. But it is also habitually expended, notably in order to bring up NES's pathophysiological mechanisms and/or possible risk/etiological/precipitating factors. And at this level and quite ironically, it seems that the characterisation of NES is done in as many varied terms as there are varied sorts of them. This leads to a certain confusion, because by doing so, they often restrict NES to a few of their facets and consequently give away by their phraseology their slightly different conceptions about what this family of disorders encompasses.

If we want to be exhaustive without describing all the peripheral nerves which can be involved in NES, the detailed definition of NES should still highlight several points :

- the different categories of "vulnerable anatomical sites" : sometimes called in a more evocative manner "anatomical bottleneck"[133], they refer to inextensible anatomical paths[146] (canals, channels, tunnels, narrow ways…)[6], more specifically osteofibrous tunnels (e.g. carpal tunnel), osteomuscular tunnels (e.g. fibular neck) or fibromuscular tunnels (e.g. scalene triangle)[138]. England slightly strays from the habitual definition by adding the possibility of deformation of the nerve by a "*fibrous band*"[147]; however these would appear at vulnerable anatomic sites as well.
- the different degrees of nerve injuries: generally classified according two different systems which convey different significances in terms of possibilities of recovery and therapeutic approach, we distinguish the neuropraxia, axonotmesis and neurotmesis according to Seddon[141] and the first to fifth degree nerve injuries according to Sunderland[148]; in the case of NES, the degree of injury is related to the severity and extent (time) of the compression[149].
- the risk/etiological/precipitating factors at play for the onset of nerve injuries: Pecina et al. distinguish the intrinsic (internal to the nerve trunk) or extrinsic (external to the nerve trunk) causative factors, and mention notably structural anomalies (e.g. cervical rib), metabolic (e.g. diabetes, hypothyroidism), hormonal (e.g. pregnancy), tumoural (e.g. Schwanoma, apical lung tumours), inflammatory (e.g. viruses, bacteria, rheumatic diseases), iatrogenic (e.g. casting, surgical trauma) and vascular (e.g. arteritis, aneurysm)[6] aetiological factors. But this list, if not exhaustive, appear at least to be

* for it highlights only the clinical aspect of NES

possibly refine. Blancher and Kubis note that in most of the cases of NES, purely mechanical factors are at the origin of the symptoms, the mechanical forces refer mostly to compression but also to stretching or traction, angulation or friction[135,147,148].
- the pathophysiological mechanisms of injury: more or less extensively evoked by authors and with frequent omissions, they encompass the theories of acute and chronic compression inducing ischemia, traction or stretch inducing ischemia, repetitive microtrauma[149], vibration[150], primary vascular compromise, and the double crush mechanism.

Perhaps more confusing than their general definition, is the multitude of denominations that are interchangeably used by authors talking about this group of focal peripheral neuropathies[*]. Nerve entrapment syndromes, nerve compression syndromes, tunnel syndromes or canal syndromes are considered to synonymously refer to the lesion of peripheral nerves at vulnerable anatomical spaces. But these different appellations almost inadvertently emphasise different features of theses disorders : the pathophysiological mechanisms (compression/entrapment) or the correlation between the vulnerability of some structures at a specific site and the development of a lesion (canal/tunnel). And these characteristics, because they are of different relevance from one NES to another, are more or less clarified in the dedicated literature. Besides, the notion of NES is submitted to slight alterations when it comes to cross the language barrier, adding to the difficulty of apprehending this global concept. For instance, as observe Bard in a 2007 French publication, the French terminology for NES suggests a slightly less restrictive view of this group of disorders[146]. Indeed, the denomination "syndrome canalaire", literally translated by "syndromes occurring in anatomical canals" does not exclude the possible involvement of the structures that frequently accompany the nerves during their course, namely the veins and arteries. Even so, this omission carries few consequences[*], as in a majority of cases, it is the affection of nervous tissue which is first symptomatic[146]. This possible involvement of the neurovascular bundle as a whole is however sometimes mentioned in the English literature and notably by Pecina and colleagues who chose to broadly define NES as *"syndromes all originat[ing] from a lesion to neurovascular elements in a narrow anatomical space"*[6]. And regarding the type of NES on which we have chosen to focus, i.e. the TOS, this addition to the general definition of NES takes on its full meaning, as

[*] which do not result from acute trauma or which do not evolve into multifocal neuropathies
[*] but is worth being mentioned as we chose to exemplify NES with the case of the TOS

the TOS is generally defined as the pathological expression of the compression of the neurovascular bundle that travels through the thoracic outlet.

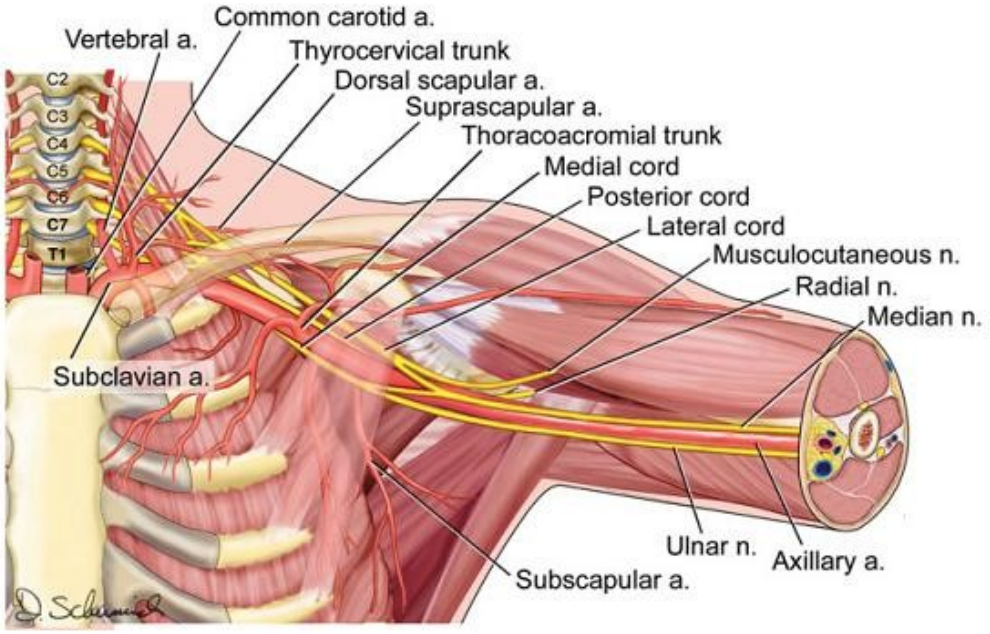
4.2. Specific anatomical and etiologic features of the thoracic outlet syndrome and general pathological mechanisms involved in the onset of nerve entrapment syndromes

If all NESs give rise to analogous and stereotyped symptomatologies (because of the similarity of the affected structures, i.e. peripheral nerve trunks or plexuses), they are also related by their general pathophysiological mechanisms causing the development of symptoms. But on the other hand, there is one domain in which all NESs (and sometimes their subgroups) show dissimilar features: the site of the entrapment and consequently the factors leading to impairment of this region. In this section and the following ones, we propose to exemplify these particularities with the case of the TOS; starting by describing its anatomical features we will pursue by unveiling its argued etiological factors. In a last section, we will explain the pathophysiological mechanisms which are applicable to the NESs generally and thus also are to the TOS.

4.2.1. Anatomical features of the thoracic outlet syndrome

Malas and Ozcakar have rather well crystallised the concept of TOS by defining it as the *"complex of signs and symptoms that is caused by compression of the brachial plexus and subclavian vessels in the cervicoaxillary region"*[151]. In this context, the term thoracic outlet refers anatomically to the space comprised between the manubrium sternum anteriorly, the left and right first ribs laterally and the first one or tow thoracic vertebrae posteriorly. Because this term can lead to confusion (notably with the lower thoracic aperture), it is synonymously used in targeted literature with the appellation "cervicoaxillary" or "cervico-thoraco-axillary space"[152]. As notice Hachulla et al. this space is physiologically narrow (as a result of the humankind's transition to the erect posture) and sometimes significantly shrunk during everyday life movements[153]. It is not an enclosure in its strict sense but rather a bony boundary through which travels the

neurovascular bundle formed of the brachial plexuses and subclavian and axillary arteries and veins[148]. In that sense, the TOS is named, as a variety of other NESs, after the problematic anatomical site[6]; but unlike most of them, its mere denomination in fact conceals its multifaceted anatomical causes[154].



Picture 13- The brachial plexus and its neighbouring arteries, reproduced from *Brachial plexopathies: classification, causes and consequences* By Ferrante, 2004.

As they travel through the cervical and axillary region, the courses of the brachial plexus and subclavian and axillary vessels are closely related. The subclavian artery arises from the arch of the aorta on the left and from the brachiocepahlic artery on the right. It ascents into the neck before arching laterally to become the axillary artery at the lateral border of the first rib; it is overall situated below the clavicle[155]. The subclavian vein extends from the axillary vein and runs from the outer border of the first rib where it follows the subclavian artery[148,155]. The brachial plexus defines a triangular shaped structure extending from the spinal cord to the axilla on about 15 cm. It is composed of connective tissue and neural tissue in a 2 to 1 ratio[156] and is classically described as comprehending five roots (classically C5 through T1), three trunks (upper, middle, and lower), six divisions (three anterior, three posterior), three cords (lateral posterior and medial and several terminal nerves (see picture 13)[133]. The anterior rami that form the brachial plexus emerge from between the anterior and middle scalene (that form the scalene triangle or groove); at this level they are accompanied by the subclavian artery while the subclavian veins travels anteriorly to the anterior scalene. In

the scalene triangle, the anterior rami occupy most of the vertical dimension while the subclavian artery travels in the subclavian groove of the clavicle[157]. The brachial plexus's trunks are located behind the clavicle and the sternocleidomastoid muscle and their lower component lies adjacent to the subclavian artery and the apex of the lung. In their anterior and posterior divisions, the upper, middle and lower trunks follow a retroclavicular course before they divide below the pectoralis minor into cords which are bound to the second segment of the axillary artery. The lateral, posterior and miedial cord therefore lie in the proximal region of the axilla, near the axillary lymph node chains and major blood vessels to the arm. Finally, the cords give rive to five terminal nerves which form at the direct exit of the axilla[133,156].

As these reminders of anatomy can lead one to suspect, impairment of the neurovascular bundle may take place at more than one site during its course through the thoracic outlet. Authors classically distinguish three critical regions which are the scalene triangle, the costoclavicular interval and the coracoid-pectoralis minor loop (see picture 14)[158,159,160]. Other possible but less frequently mentioned regions of neurovascular involvement include the vicinity of the suprapleural fascia, the clavipectoral region and anteriorly to the humeral head[161]:

- the scalene triangle, also called scalene groove is formed by the anterior and middle scalene muscles laterally (typically attached about 2 cm apart)[148] and the first rib caudally ; the shape of the triangle is variable (cervical rib, body built, variations of the muscles themselves with hypertrophy, anomalies, supernumerary muscles, fibrous band…) and a compression in this area typically causes symptoms consistent with C8 and T1 involvement[143,157]
- the costoclavicular interval defines the vice-like bony interval between the clavicle and the first rib through which travel the axillary vessels and the brachial plexus[157]. As the clavicle is depressed during depression and posterior displacement of the shoulder (for instance while carrying heavy bags, or when wearing a heavy backpack), the costoclavicular space is narrowed and despite the separation of the neurovascular bundle from the clavicle by the subclavius muscle, the provided protection remains minimal[157]. The costoclavicular space is typically in cases of poor posture with dropping shoulders, or because of changes in sizes of either bones (for instance after a fracture of the clavicle). Its narrowing seems to affect more the lower brachial plexus over the upper one, and especially the subclavian veins as it is closer to the peak of the triangle

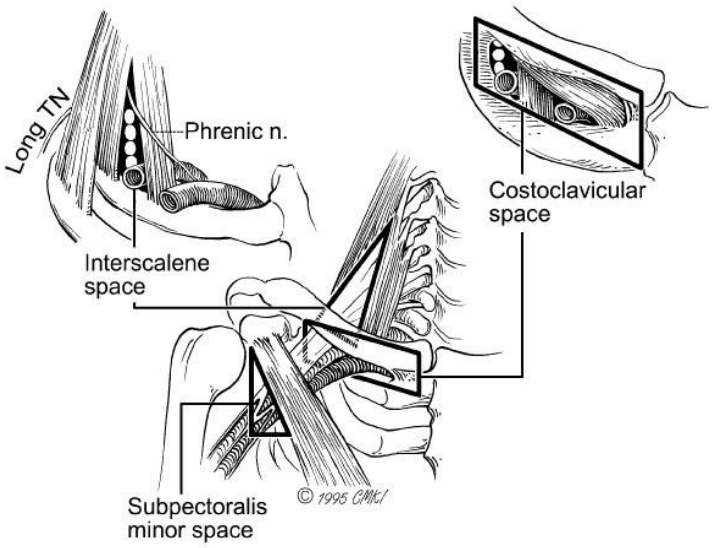
formed between the clavicle and the first rib (which can evolve into a Paget-Schroetter syndrome)[148].

- the coracoid-pectoralis minor loop, also called retropectoralis minor space, refers to the point where the brachial plexus, surrounding the axillary artery and bound with the vessels by the fascial axillary sheath, passes beneath the coracoid process and posterior to the tendinous insertion of the pectoralis[157]. At this level, combined abduction and external rotation causes the neurovascular bundle to stretch around the coracoid process, however without slipping over it as this is prevented by the pectoralis minor tendon. In addition to a possible obliteration of the artery, the brachial plexus is typically affected in its lower trunk (C8 and T1 distribution) by this mechanism[148].

- the vicinity of the suprapleural membrane[161], also called Sibson's fascia (attaching at the transverse process of C7 and the internal border of the first rib) defines another possible site of involvement of the neurovascular bundle. It is poorly addressed by the English literature but more frequently mentioned in the French one (under the denomination "appareil suspenseur de la plèvre" which can be literally translated by "upper attachment of the parietal pleura"); this probably êrtains to the fact that this anatomical structure has been described by different authors, notably Zuckerlandl and Sebileau which are more known of the French medical corps[162].

- the clavipectoral region defines the area where the costoclavicular ligament is in direct contact with the subclavian vein and therefore can participate to its compression[161].

- the humeral head's anterior region is in direct contact with the axillary artery and the terminal branches of the brachial plexus and pushes them forward and elongates them during combined movements of abduction and posterior displacement of the shoulder[161].



Picture 14 - The three major anatomic regions which are hypothesised to contribute to neurovascular lesion in the thoracic outlet, reproduced from *History of thoracic outlet syndrome*, by Atasoy, 2004.

The recognition of these different ways of impairment of the neurovascular bundle that travels through the cervico-thoraco-axillary space and of its possible levels of injury is at the origin of a primary etiological classification of the group of TOSs. It distinguishes the scalenus anticus syndrome, the costoclavicular syndrome, the pectoralis minor syndrome but also the hyperabduction syndrome, the cervical rib syndrome or the first rib syndrome. However, this classification is nowadays more or less dismissed for a more symptomatology-oriented one that distinguishes the involvement of the neural, arterial or venous structures. It will be discussed in the next section (4.3.)[159].

4.2.2. Predisposing and etiological factors of the thoracic outlet syndrome

As for several other NESs[6], various etiological factors have been defined for the TOS and are more or less extensively reviewed in the general literature. Classically, symptoms are thought to result from the alteration or narrowing of the thoracic outlet and a variety of factors have been claimed accordingly[163]. In a recent publication, Laulan et al. divide these etiological factors into four broad categories[164], namely, the congenital abnormalities, the post-traumatic causes, the functional or acquired causes, and others acquired causes. Hachualla et al. expand this inventory by adding what one could term as individual factors and which could rather be considered as predisposing than causative[153] :

- individual factors : either gender-, age- or morphotype-related, their incrimination as predisposing factors pertains to the observation of the higher incidence of TOS in subgroups of populations. First in women, the particular orientation of the first rib (more vertical) and a more upper thoracic breathing pattern would predispose them more than men to this disorder. Secondarily, it has been observed that the syndrome particularly affects individuals between 30 and 50 years old; Hachulla et al. notice in this respect that the lowering of the thoracic wall until puberty takes the clavicle dorsally and caudally, which explains why the TOS is rare in children; according to them, age would predispose to the settlement of a muscular atrophy of the shoulder girdle muscles which would result in the narrowing of the costoclavicular space.

Finally, they observe that for an important number of TOS sufferer, the slender morphotype prevails[153].

- congenital abnormalities : they can be associated with traumatic or functional causes and encompass bone, muscular, and fibrous anomalies (the latter accounting for 2/3 of the anomalies detected at operating) [164]. We can generally quote the anomalies of the transverse process of the seventh cervical vertebra, the cervical rib (either consisting in an hypertrophy of the C7 transverse process, rudimentary with free extremities, incomplete but connected to the 1st rib by a fibrous band or completely fused with the 1st rib by a cartilaginous pseudoarticulation)[165,166], a first rib, a scalenus anticus muscle, a sickle shaped scalenus medius, or anomalies of the costoclavicular ligaments, subclavius muscle or pectoralis minor[163].

- the post-traumatic causes : either at the area of the soft tissues or bones and notably after motor vehicle incident or sporting incident, they typically encompass the wishplash injuries, falls, lifting injury affecting the neck or shoulder and sometimes some upper limbs traumas (weight fell on the shoulder or arm)[167]. Bone remodelling after fracture of the clavicle or the first rib producing a voluminous osseous callus can also cause a TOS; its onset in such cases is thought to be possibly delayed as much as 2 years after the trauma[164].

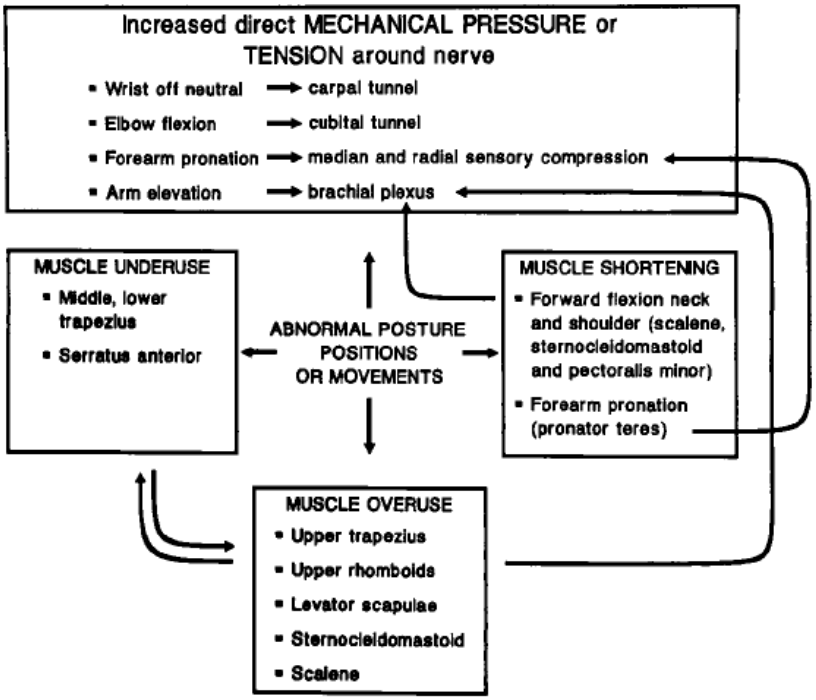
- the functional or acquired causes : postural anomalies, notably shoulder protraction[168] or dropping, upper thoracic kyphosis, and winged scapulae[169], muscle imbalances with hypertrophic muscle of the cervicoscapular region, incorrect breathing pattern with hyperrecruitment of the accessory muscles of the respiration and more generally repetitive movements and certain working positions (notably in professions requiring frequent arm elevation such as hair-dressers, assembly lines or in which is adopted anterior flexion of the shoulders and head such as secretaries, computer workers) are thought to cause the onset of TOS[164].

- other acquired and secondary causes : they are more rare but, because of their diagnostic and clinical importance, must be systematically considered ; they encompass amongst others tumours (extrinsic as for apical lung tumour or intrinsic), hyperostosis/exostosis (i.e. excessive growth of bone), and osteomyelitis (i.e. infection and inflammation of the bone or bone marrow[164].

Going into the functional aetiology of the TOS in depth, Novak and McKinnon have theorised how dynamic and static posture (i.e. repetitive movements and prolonged

positions, notably of *"the head, neck and upper limbs assumed at work or during sleep"*) may impair the nerve trunks and plexuses[160,170] . They define for these types of postures three major deleterious effects (see picture 15) :

- a direct increased pressure on nerve entrapment sites; for instance in the case of the TOS, arm elevation increase tension on the brachial plexus.
- a placement of some muscles in shortened position which trigger adaptative shortening and hypertrophy and eventually results in nerve compression; as frequently seen in the TOS, head protraction with thoracic increased kyphosis and scapular abduction eventually results in sternocleidomastoid, scalene and suboccipital but also serratus anterior and pectoralis minor muscles adaptative shortening and an attempt of correction of this posture increases the pressure on the brachial plexus at the level of the interscalene triangle or beneath the pectoralis minor.
- a placement of other muscles in elongated and weakened positions, which results in the overuse of others and eventually create a cycle of muscle imbalance; still for the TOS, the aforementioned posture results in the elongation of the trapezius muscle and compensatory overuse of other muscles (longus and longissimus cervicis, the levator scapulae and the major and minor rhomboids, the lower trapezius scapular muscles)[171]



Picture 15 - The cycle of muscle imbalances and its pressure or tension effect on the nerves, reproduced from Repetitive use and static postures: a source of nerve compression and pain, By Novak and MacKinnon, 1997.

4.2.3. General pathophysiological mechanisms at play for the TOS and more generally for the nerve entrapment syndromes

As, when introducing NESs in general, authors often merge pathological mechanisms and etiological factors, it does not seem superfluous to make a clear distinction between them. The etiological factors in fact account for the origin of a disorder, as we could observe for the TOS, but also for a majority of NESs, they are extremely numerous and sometimes remain unknown. The physiopathological mechanisms on the other hand embrace the means and reactions of the body to exposure to these etiological factors and are the same for all types of NESs. However, according to the different etiological factors, the body adapts slightly differently, in other words, the pathophysiological mechanisms are slightly different.

In the case of NESs in general and TOS in particular, authors consider that mechanical factors and especially compression are chiefly at the origin of the symptoms[136,138] and accordingly describe the pathophysiological mechanisms at play. According to its acute or chronic character, the compression leads to a cascade of histopathological changes at the level of the nerve trunks or in its surroundings, which interplay on one another (see picture 16):

- the acute nerve compression first compromises the intraneural circulation (perineurial blood flow) and the axonal transport resulting in ischemia[137,172]. These pathological change would start occurring for as low as 20-30mmHg, pressure, which are, as Blancher et al remind us, about the same range of pressure observed in maximal flexion of the wrist for instance[138]. This ischemia further causes an inflammatory response in the nerve trunks (mediated by neuropeptides released from the mechanically irritated nervi nervorum and pro-inflammatory mediators produced by immune cell activation) and dorsal root ganglions. The inflammatory response results in oedema at the level of the endoneurium and epineurium and reactively an increased pressure in the fascicle[137]. The oedema persists as there are no lymph vessels in the endoneurial space to drain it and this oedema further restricts the blood and axonoplasmic flow[137,173], interfering with the axon function (i.e. possibly reducing the capacity of repair and regeneration of the distal axon) [136] despite the axon being physically intact[172]. It is interesting to notice that Fern et al. have demonstrated that this acute type of compression is more likely to first

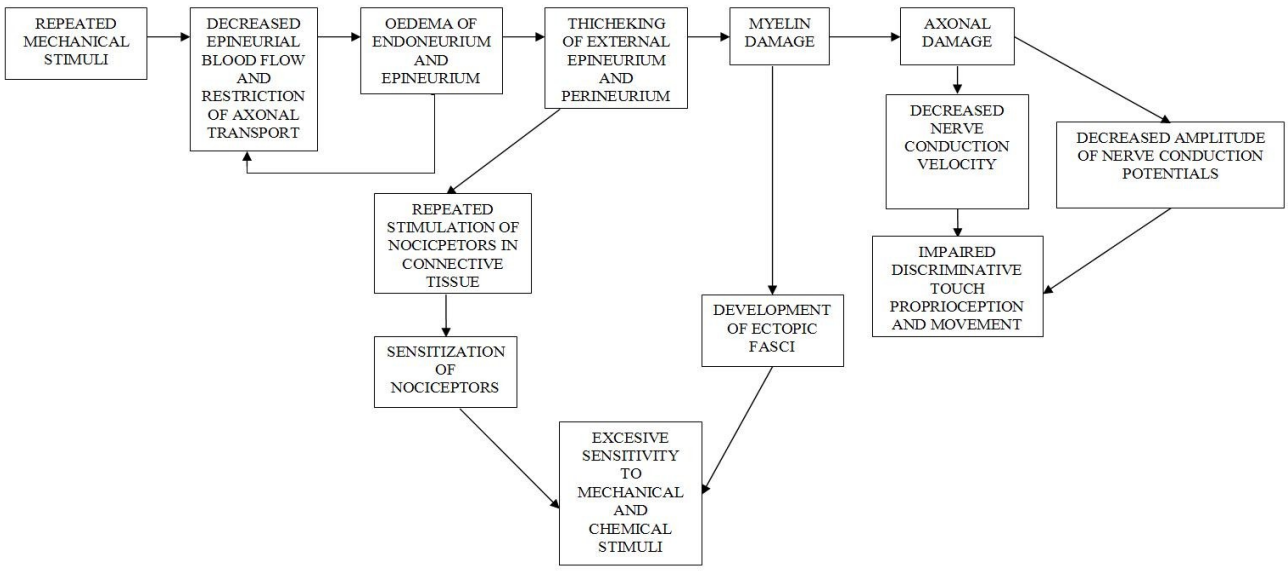
produce deformation of the myelinated fibres with rapid conduction speed (i.e. classically motor fibres)[174].

- the chronic nerve compression involves a persistent endoneurial oedema favoured by the increase in the permeability of the endoneurial capillaries (destruction of the nerve blood barrier) and the obstruction of the blood flow in the vasa nervosum resulting in ischemia[138]. The enodneurial oedema leads to intraneural fibrosis, decreasing the viscoelastic properties of neural connective tissues[137]. After intraneural fibrosis, follows axon and myelin change which occur successively: there is first thinning of the myelin sheath and decrease of the internodal spaces (caused by demyelination-remyelination phenomenons)[138]. This remyelination first touches the more external fibres of the nerve trunk and then spreads to the more central ones which demonstrates that the most peripheral fibres are more sensitive to compression than the most central ones[138]. There is then segmental demyelination followed by diffuse demyelination[173] which is shown by a slowing of the conduction speeds first at the level of the compression and then distally[138]. Finally perineurial thickening occurs[173]. This cascade of histopathological changes would also results in the development of ectopic foci, _also called abnormal impulse generating sites[*]_ on segments of injured peripheral nerves, which thus develop the ability to repeatedly generate their own impulses[137]. It has been theorised that signals from the myelin deficient part of the nerve alter the gene activity of the neuron cell body, which would stimulate the production of excessive numbers of mechanosensitive and chemosensitive ion channels that are subsequently inserted into the myelin deficient membrane[172]. Normally innocuous mechanical stimuli such as friction or pinching or chemical stimuli (notably adrenaline secreted under stressful conditions) would thus become nociceptive. Finally, Fern et al. have demonstrated that the chronic type and less important type of compression, causes rather ischemia of the poorly myelinated fibres with slow conduction speed (i.e. classically, the sensitive fibres)[174].

Allieu and Amara also state that for upper limb NESs, besides the mechanical compression, the mechanical traction constitutes another pathological mechanism[175]. In the case of a TOS, the traction of the brachial plexus would more likely occur at the anterior portion of the humeral head during abduction and retropulsion of the upper limb[161]. The structures of the peripheral nerves react to traction forces depending on

[*] because axons that normally just transmit impulses become capable of initiating them

how elastic and flexible they are and the degree to which they are stretched. The effects of extension depend in the kind and strength of the deformation, the duration of the effect and the topographical location within the nerve[135]. Nerves can indeed be injured by a single application of high force traction of by repeated application of lower levels traction that would not cause injury if they occurred only once. The longitudinal traction forces increase the intraneural pressure, therefore, when the nerves are stretched by more than 6 to 8% of their original length, intraneural circulation is impaired and compound motor action potentials are reduced[176]. Stretching of a nerve by more that 10 to 20% of its original length is associated with structural failure and changes in compound motor action potentials to complete conduction block. With elongation by 20 to 30% or more, the perineurial sheaths begin to rupture[176]. After intraneural tearing, there is haemorrhage and consequently intraneural scarring as a result of proliferation of fibroblast and collagen[177]. As notice Barral et al, the anatomical environment is important notably because of the possibility for the nerve of dynamic adjustment: at the interneural level (elongation of fascicles) but also by a sliding movement of the nerve within its anatomical environment. As a result, a softly embedded nerve is less prone to injury than are nerves traversing a bony process or near a joint[135]. At the level of the brachial plexus, Vasilevskis et al. found that arm abduction above 90° was sufficient to induce lesion sin neural bundles[177].



Picture 16 - Pathological mechanisms in the production of symptoms related to nerve entrapment syndromes, reproduced from *Neurosciences* by Lundi-Ekman, 2013.

Another pathophysiological mechanism put forward for upper extremities NESs and notably for the TOS is the one of the double crush syndrome[160]. This concept originates from Upton and Cormas who, before intriguing clinical, surgical and anatomical observations about CTSs cases[136], theorized in 1973 that a proximal site of compression would render the more distal sites less tolerant to compressive forces and more likely to a second site of compression. A perturbation of the axonoplasmic flow would be involved, impairing the distribution of trophic factors in the whole length of the nerve[136,].

Going back to the most commonly argued pathological mechanism for NESs, namely the mechanical compression, it appears that the greater its force or duration, the greater the oedema formation and sustained neural pressure[173]. Moreover, at same duration of compression, recovery is less good with more intense forces of compression, and the lesions can persist till three weeks after her decompression[138]. Also, Novak and McKinnon also note that the histopathologic changes may not occur evenly across the nerve and that fascicles located superficially may be affected first[170]. These observation leads us to wonder about the degree of severity of the nerve injury resulting from compression but also traction, double crush or other mechanisms. Two systems are most commonly used for the classification of nerves injuries, the one of Seddon and the one of Sunderland[6,140]. The classification of nerve injuries according to Seddon (see table 12) was originally proposed for external trauma such as superficial or penetrating nerve injuries but also generally applies to NES[140]; it generally distinguishes the neuropraxia, axonotmesis and neurotmesis. According to this same author, a NES could only produce a neuropraxis or eventually an axonotmesis but complete disruption of the nerve do not occur in NES[6]. The classification of Sunderland expands the one of Seddon by subdividing the neurotmesis in three other classes according to the degree of damage to the epineurium, perineurium and endoneurium.

TYPE OF LESION	ANATOMICAL AND ELECTROPHYSIOLOGICAL FEATURES	RECOVERY OUTCOME
NEUROPRAXIA	- focal myelin compression, endoneurial sheath intact - Slow or no conduction across lesion, normal conduction distal to lesion, no denervation, decreased or no voluntary motor units	- good, complete and rapid by remyelination - the conduction velocity, if initially slowed because of associated demyelination, returns to normal with remyelination

Table 12 - nerve injury classification according to Seddon, modified from *Color atlas of neurology* by Rohkamm, 2004 *and Neuroscience* by Lundy-Eckman, 2013

AXONOTMESIS	- physiologic disruption of axon, endoneurial sheath intact - Slow or no conduction across lesion, no conduction distal to lesion, denervation activity, decreased or no voluntary motor units	- poor and slow by regrowth of axons (regeneration at 1-2mm/day proximally, more slowly distally) from proximal to distal along the enveloping structures
NEUROTMESIS	- anatomic separation of nerve and endoneurial sheath - no conduction across lesion, no conduction distal to lesion, denervation activity,	- poor to none with greatly limited axon regeneration in the absence of surgery - anomalous regeneration and neuroma development are common

Table 12 (Continued) - nerve injury classification according to Seddon, modified from *Color atlas of neurology* by Rohkamm, 2004 *and Neuroscience* by Lundy-Eckman, 2013

4.3. Symptomatolgy: clinical manifestations associated with the thoracic outlet syndrome

4.3.1. About the clinical presentation of nerve entrapment syndromes in general and of the thoracic outlet syndrome in particular

The primary symptomatologic feature of all NESs is indubitably the pain[6], which, by evoking a neurological pathology with its topographic and other specific features, makes the symptomatology of this group of disorders already quite stereotyped[146]. Neuropathic pain is often described by NESs sufferers as sharp, shooting, irradiating, burning, tingling or electric-shock like in its character and may be present at all times, worsen with motion and wake one from sleep[6,146]. It is commonly accompanied by a constellation of complaints conjuring up the involvement of sensory, motor, autonomic or (usually) mixed nerve fibres. In the former case, the patient may present notably parasthesias (i.e. spontaneous or evoked abnormal sensation[141]), dyesthesias (spontaneous or evoked unusual or unpleasant sensation[141]), hypoesthesias (diminished sensitivity to a non-noxious stimulus, commonly termed as numbness[141]), hypalgesia (diminished sensitivity to a painful stimulus[141]), hyperesthesias (increased sensitivity to stimulation[141]), hyperalgesia (increased response to a painful stimulus[141]) and loss of discrimination sense[6]. Motor fibres involvement is reflected by the setting up of a paresis of flaccid type of the muscles innervated by the affected nerve and thus characterised by muscle weakness and hypotonia with light diminution to absence of

tendon reflex[133]. Finally, because the sudomotor fibres travel together with the somatosensory components of the peripheral nerves, diminished sweating is often found in the hypoesthetic area of skin and autonomic abnormalities of other kinds (i.e. vegetative disturbance) may also be present in the distribution of the affected nerve (in contrast, radicular lesions generally does not affect sweating) [133]. However a majority of peripheral nerves are mixed (i.e. motor and sensory) and their impairment results in combined and varying effects among the range of aforementioned signs[138]. Besides, as notice Pecina et al, nerve entrapment of any type can be present with symptoms proximal and distal to the actual area involved and complaints often range from vague or diffuse pain to specific complaints of muscle weakness or of sensory changes over localized skin areas. Moreover, in most cases, sensory symptoms and signs usually appear before motor signs[6].

Blancher echoes these observations by claiming the existence of a certain degree of clinical polymorphisms in the different NESs, regardless their topographic attributes[*] [138] . This view takes on a broader and slightly divergent meaning in two ways in the case of our NESs' example. Firstly, a variety of symptoms pertaining to the impairment of the neurovascular bundle have been described for the TOS: primary pain or sensation of heaviness and fatigue in the shoulder and neck region, usually accompanied by paresthesias radiating from the shoulder to the ring and little finger, but also associated CTS (double crush phenomenon hypothesized), Raynaud's phenomenon, reflex sympathetic dystrophy, tendonitis, bursitis or adhesive capsulitis…[178] . Secondarily, if, as we have demonstrated above, the TOS can be categorized according to its different etiologies (cervical rib syndrome, scalenus anticus syndrome…) it also can be categorized symptomatically, namely according to the affected structure of the neurovascular bundle[179]. Indeed, one must not forget that the denomination TOS refers more to a group of affections of the brachial plexus and vessels as they travel through the cervico-thoraco-axillary space, rather than to a mere focal peripheral nerve disorder[151]. The symptomatology associated with vascular compromise although less frequent in NESs[*], is as much stereotyped as the one associated with peripheral nerve injury and even more unequivocal: throbbing pain and limb discoloration (bluish or white), swelling, fatigability, or weakness are very good indicators. Three subtypes of TOS, with different prevalences amongst TOS sufferers, are thus classically

[*] which he partially explains by the general pathomechanisms of nerve compresion (see 4.2.3.)
[*] in this case definitely the naming tunnel syndrome appears more appropriate

distinguished: the venous TOS, the arterial TOS, and the neurogenic TOS. If the alleged figures of prevalence for each of them slightly differ according to the publications, they nevertheless converge towards the same observation : the vascular (arterial and venous) types are by far the least common, whereas the neurogenic type represents the wide majority of TOSs[158].

4.3.2. The vascular types of thoracic outlet syndrome

The vascular types of TOS, i.e. arterial and venous, are considered to be much least common than the neurogenic one. Argued figures for the arterial type range between less[180] than 1%[181], to 2,1%[182]. and even 5%[183] and between 1,8%[182] to 5%-8%[153] and even 10 to 15%[183] for the venous types. As for him, Atasoy states that for the TOS in general, *"The compressed neurovascular structures in decreasing frequency are the brachial plexus (90%), the subclavian vein (6-7%) and the subclavian artery (3-4%)"*[158]. The venous structures would thus be more likely to be compromised than the arteries within the framework of a TOS. However, Watson et al, who go by two studies realized by Davidovic et al. and Singh state that it is the arterial involvement which is more common than the venous involvement[184,185]. In fact, if the compression of the subclavian artery, intermittent, is indeed frequently found in the TOS, the onset of complications related to such a compression (i.e. symptomatic arterial TOS) remains for its part exceptional[153]. More still, for Becker and Terriat, the overall vascular compressions occurring in the thoracic outlet are largely asymptomatic[186] and postural vascular anomalies are incidentally frequent (between 30% and 60%) in subjects who do no present any functional symptomatology[186].

That being said, in rare instances, the TOS takes on an arterial symptomatology because of the compression of the subclavian or axillary artery. If it is, according to Roos, the rarest type of TOS, it is also the only one that is seen in equal proportions in both genders[186]. And according to Thompson, the arterial involvement is usually associated with anatomical anomalies such as cervical rib or band[183]. The symptomatology is then the typical one of an arterial insufficiency[187] , as Sander et al. describe it: *"the symptoms of [arterial] TOS include digital ischemia, claudication, pallor, coldness, paresthesias and pain in the hand but seldom in the shoulder or*

neck"[180]. Hachulla add to this set of signs the possible but extremely rare onset of spark-like hemorrhages under the nails, infarction around the nails or even gangrene of the fingers[153]. In fact, intermittent effort claudication is only found when there is axillary thrombosis (forming just distal to the subclavian artery stenosis) or if there is embolic subclavian aneurism[153,180]. The observation of a Raynaud's phenomenon in arterial types of TOS is somehow contentious; Hachulla et al. state that a unilateral Raynaud's phenomenon can be the only clinical manifestation of the arterial involvement and its onset can be explained by a chronic irritation of the peri-arterial sympathetic plexus at the suclavian level[153]. However, according to Becker et al. who refer to three publications of Carpentier (1998), Grassi et al. (1998) and Reggi et al. (1979), no statistical relationship between the Raynaud phenomenon and the TOS has yet been established188,189,190. Finally for Sanders, the pallor and coldness of the involved limb are rather due to ischemia than to a Raynaud's phenomenon[180].

The venous type of TOS, thought to be more frequently encountered than the arterial one (at least in operating rooms), is set apart from the latter and the neurogenic type by its higher frequency in men[189,186,191]. It affects usually the dominant limb[191] and, similarly to the arterial type, it presents a very characteristic symptomatology of which pain, oedema, and cyanosis constitute the cardial features[180]. The pain or aching is often present but may also not be related by the patient. The edema or swelling, happening acutely, represents a characteristic feature of the venous TOS, as it is not seen in the arterial or neurogenic types[180]. It can lead to secondary paresthesias in fingers and hands[180]. A sensation of heaviness of the arm is also often reported and over time, the collateral veins will appear more prominent (see picture 17)[187]. The obstruction of the subclavian vein can be either thrombotic or non-thrombotic[180]. For Thompson et al. three important factors participate to the onset of a venous TOS : the hypertrophy of the pectoral muscles, a thickening and fibrosis of the vein's wall caused by repetitive traum a and finally an impair-

Picture 17 - Typical appearance of a venous TOS with dilated superficial veins, reproduced from *Venous thoracic outlet compression and the thoracic outlet syndrome* by Thompson et al., 2011.

-rment of the intima of the vein which becomes rough and thrombogenic on its surface[191]. In 3% of cases of venous TOS[186], the venous compression is complicated by a thrombus, namely by the onset of a Paget-Schroetter syndrome or effort venous thrombosis. The onset of this syndrome is precipitated by an episode of increased physical activity, and often by factors leading to higher blood viscosity, such as dehydration and the oral contraceptive pill[191]. It is estimated that 10% of these thrombotic venous TOS will evolve into a pulmonary embolism[191]. For Becker and Terriat, further risk of pulmonary embolism is excessively rare and the direct resposability ot the primary TOS is uncertain[186].

4.3.2. The neurogenic thoracic outlet syndrome

The general consensus is that the neurogenic TOS, i.e. the impairment (by compression or irritation[183]) of the brachial plexus, is considered to by far the most common with alleged figures such as 85, 90, 95, 97% or 98%[183158,155,187,192,186] . It affects more women than men with a sex ration of 2 to 3 for 1[185,186]. In general, it can produce a constellation of symptoms : pain and paresthesias of the ispilateral cervical, supraclavicular, intersubscapular regions and upper limb[151], edema, headache, sympathetic nervous system impairement (under the form of pseudoangina, complex regional pain syndrome, hyperhydrosis, Raynaud's phenomenon…[182])[192]. In more advanced cases, muscle atrophy can be seen along with loss of fine motor control[187]. The pain represents the foremost feature of the neurogenic TOS can seriously impact TOS sufferers' quality of life[192]. The pain can originate either from the somatic fibres C5 to T1 or from the afferent sympathetic nerve fibres, which transmit deeper painful stimuli and which impairment results in referred pain[182]. The symptoms are exacerbated by movements, notably arm elevation (e.g. hair combing, working overhead, painting, upholstery, housework) or when carrying heavy objects[192]. Malas and Ozcakar, going by some of their previous studies report additional and noteworthy symptoms : tachycardia, dyspnea, dysphagia, vertigo, dizziness injury for the two and tinnitus which can possibly be observed in TOS sufferers[151]. Urschel relates the onset of vertigo and dizziness but also blurred vision rather to upper brachial plexus involvement. Orset also notices that for in most chronic cases of TOS, are frequently found cervicalgia,

scpulohumeral disorders, notably capsulitis, trigger points, and sometimes even signs of irritation of the axillary, subscapullary or intercostal nerves[168].

	TRUE NEUROGENIC TOS	UNSPECIFIC TOS
CAUSE	- irritation, compression or traction of the brachial plexus creating compromised nerve function - compression usually occurs via a bony or soft tissue anomaly present congenitally, created by either repetitive of significant trauma and often influenced by postural, occupational or sporting factors	- usually no bony or soft tissue anomaly can be demonstrated - intermittent compression of the neurovascular complex due to repetitive postural, occupational or sporting forces that create temporary compression at varying sites in the cervical or thoracic outlet
SIGNS AND SYMPTOMS	**Upper plexus syndrome (C5, C6, C7 pattern, Erb-Duchenne like-palsy) :** - lateral and cervical descending pain - irridiations on the external aspect of the upper limb - hypoesthesia on the territory of the radial nerve - paresthesis in the hand on the territory of the musculocutaneous or median nerve (rare) - weakness of extension of the the elbow, wrist and hand - positive Tinel signs at the subclavian level **Lower plexus syndrome (C8,T1 pattern) *Kumpke- like palsy* :** - pain in the posterior aspect of the arm - irradiation on the posterior aspect of the shoulder, in the axilla and internal aspect of the upper limb - hypoesthesia in the territory of the cubital nerve - paresthesia of the 4th and 5th fingers - weakness of the hand and interosseous muscles - positive Tinel sign at the supra and subclavian level	- predominantly neurological, intermittent and transient in nature - paresthesia in digits (variable distribution) on awakening Distal symptoms ranging from pain, aching, spasm to tingling, numbness and tightness - feeling of tenderness, swelling or loss of motor control - pain in forearm, hands and wrist - more or les pain in lower neck and shoulder, elbow, and upper back, especially over pectoralis minor, lateral humerus, suprascapular and medial scapula regions - more or less concurrent pain and headache - pain aggravated by repetitive, suspensory or sustained overhead forward elevation of the shoulder and activities that depress the shoulder girdle - pain at rest and night pain

Table 13 - Clinical presentation of true neurogenic and non specific neurogenic thoracic outlet syndromes, modified from *Thoracic outlet syndrome part 1: clinical manifestations, differentiation and treatment pathways*, by Watson, Pizzari and Balster, 2009 and *Les syndromes de la traverseée thoracobrachiale* by Merle and Borrelly, 2004.

The neurogenic TOS is further subdivided into two groups : the true (neurogenic) TOS and the non-specific (neurogenic) TOS[159,192]; the first group encompasses patients harbouring true or classic signs and symptoms and EMG findings (true neurogenic TOS); thus characterized by the objectivity of the clinical findings it would account only for 1% of all the neurogenic cases[192]. The second group gathers 99% of the other neurogenic TOS sufferers[192], that is, the vast majority who do no present specific clinical and EMG findings (unspecific neurogenic TOS) and for which clinical observations remain subjective and thus controversial[159]. We distinguish furthermore two clinical presentations of the neurogenic TOS (in general or only for the true one according to authors). The upper plexus impairment typically involves symptoms mostly in the arm and forearm, but sparing the hand; additionally, there is possibility of neck, ear, face and occipital pain. The lower plexus impairment typically

involves symptoms of the hand (paresthesia in the 4th and 5th digits) but with usual sparing of the arm and forearm[187]. The neurogenic TOS in that sense differs form a typical NES as the symptoms distribution does not follow specific peripheral nerves innervation territory. But is indubitably differs from cervical radiculopathies for it is usually not limited to a specific dermatome[187]. A summary of the features of the neurogenic groups of TOS is presented above in the table 13.

4.4. The uncertain epidemiology of the thoracic outlet syndrome

The overall incidence of NESs has reached according to some, "nearly epidemic" proportions[193]. For instance, the indubitable "star" of this group, the CTS, has an estimated incidence of nearly 1% annually in the USA, which makes almost 2,8 millions new cases per year[194]. In our example however, much less definitive figures have been advanced and the overall incidence of the TOS remains uncertain. Though some authors venture on providing their readers with estimations, the discrepancies of the rates they put forward make them poorly reliable; Tikli et al, for instance, state that TOS is a rare condition, probably occurring in the general population with an incidence of 1 per million[195] Watson et al. argue that the incidence would be of approximately 8% in the general population[163] while Dubuisson et al. observe that some tend to think that TOS could explain around 10% of the painful arm syndromes[167]. Thus, as the latter authors do, it seems more appropriate to only settle for observing that TOS is said to be overdiagnosed by some and underdiagnosed by others[167]. In this respect, Becker and Terriat try an interesting scholastic analogy : comparing the TOS to these forgotten schoolchildren, sitting in the end of the classroom, easily incriminated without proves and being listened to only when they manifest themselves, they symbolize the diagnostic issue that represents the TOS[186].

What is generally conceded in the literature and better known than the actual incidence of the TOS, is the most likely populations to develop this syndrome : the majority of cases are diagnosed in people ranging from 20 to 50 years old., and its onset is rare in adolescents and exceptional in pediatric populations[196]. Overall, the disorder would preferentially affect women with a 2 to 4:1 ratio[196]. Logically, under its preponderant neurogenic form it would affect preferentially women in their 20-50s

years old, ; it would affect more males in their 20-30 years old under its nervous form and indifferently both genders between 20 and 30 years old under its arterial form[181]. Occupational factors have also been outlined as participating to the onset of TOS. Reviewing the epidemiological literature dealing with the relatedness of TOS onset and occupational factors, Laulan and colleagues endeavoured to determine which populations were at risks. They found out that computer users, construction workers exposed to vibrations, but also workers whose activity demands them to frequently adopt provocative tests-alike positions (hands overhead, retropulsion of the shoulder combined to rotation of the neck and suspended upper limb) were prone to develop TOS. More specifically, they quote masons, painters, forestry workers, dentists, physiotherapists, hairdressers and musicians, cashiers and secretaries[164].

4.5. The difficult characterisation of the thoracic outlet syndrome: overview on the available diagnostic means and differential diagnostic process

4.5.1. Foreword

Similarly to other NES, the diagnosis of TOS requires a pluridisciplinary investigative approach and consultation with specialists in neurology, physical medicine, cardiology and angiography may be appropriate[182]. However, on this same diagnostic standpoint, there is a gap between TOS and other NESs; it is distinct from them not by the means, the general or differential diagnosis process (which follow roughly the same lines), but rather by the controversy that surrounds the very reality of this syndrome; first, because of the banality of the symptoms, which can be commonly experienced by the general population after certain activities (this pertains to the fact that, as a result of the Human's evolution towards an erect position, the cervico-thoracoaxillary outlet is physiologically narrow)[153]. Secondarily, because the syndrome's detection itself lacks of objectivity; in the words of Atasoy: "*because of the lack of objective findings in many TOS cases, some physicians have denied the existence of neurogenic TOS, and it has become a very controversial subject in medicine. Many*

surgeons believe that TOS is one of the most underrated, overlooked, and misdiagnosed conditions"[158]. Watson et al., share this analysis and write: *"opinions in the literature about TOS vary in the extreme, swaying from the belief that it is the most underrated, overlooked and misdiagnosed peripheral nerve compression in the upper extremity, to questioning whether it exists"* [163]. Indeed, as we have observed in the previous section, about 99% of the neurogenic types (which itself is thought to roughly represent 90% of all the TOS types) do no present any objective signs of brachial plexus impairment. Moreover, there is no pathognomic provocative test for the neurogenic type of TOS[192] and certain provocative tests commonly used for the diagnosis of the vascular type of TOS are found to be positive for pulse obliteration in broad proportions in the healthy; as false positive are legion they are regarded as unreliable[192]. Consequently, the diagnosis of the TOS remains essentially clinical and is largely one of exclusion[163,183,197].

4.5.2. The mainstay of the diagnostic process for the thoracic outlet syndrome : the clinical examination

In line with these observations the general consensus about the diagnosis of TOS is that it requires before everything an adequate and careful clinical examination. The latter, based on the history of the patient, the physical examination and the performance of provocative tests is to be focused on the extensive research of the aforementioned symptoms, the global assessment of the neuromusculoskeletal system. Because of the interweaving of the vascular and neurologic symptomatologies, rendering the diagnosis of the condition difficult[161], it is necessarily complemented by other imaging methods. The latter which will also ascertain possible anatomical anomaly accounting for the symptoms. The clinical examination finally endeavours to determine the vascular, nervous or combined character of the disorder in order to select the proper diagnostics techniques which are to be further used on the patient[155].

The history of the patient aims at gathering informations on the localisation, type, intensity, and severity of the symptoms, their onset and evolution over time and finally alleviating and aggravating factors[171]. Vanti et al. note that specific questionnaires can be used for the evaluation of pain and disability and give the examples of the McGill and the Northwick Park Neck Pain questionnaire

respectively[171]. Watson and colleagues have described a thorough process of TOS-centred physical examination based on the postural examination (research of malalignment, focussing on the upper body), palpation of the affected limb and cervical region, active and passive movement examination (cervical spine, cervicothoracic junction, shoulder, elbow, wrist and hands, looking for hyperlaxity or to the contrary limitation of motion*), examination of muscle strength, neurological examination (motor, sensory, deep tendon reflexes**) and examination of the cervical spine in general[163]. Along the same lines, Vanti et al. advocate an accurate examination of the articular, muscular and peripheral nervous system. Respectively, their recommendations of examinations focus on the palpation and active and passive physiological and accessory test for the first rib, joints of shoulder girdle and cervical and thoracic spine; for the muscular system they recommend to evaluate the trophism, strength, coordination, and length of scalene, pectoralis minor and major, levator scapulae, sternocleidomastoid, serratus anterior, major and minor rhomboids and trapezius muscles. Finally for the nervous system, they recommend the performance of provocative tests and the examination of the sensitivity especially of vibration sense as they argue it is the first type of sensation to deteriote when nerve conduction is impaired[171].

During this clinical examination, are also usually performed several provocative manoeuvres. There is indeed no single diagnostic test that can confirm the presence of a TOS[160,187]; moreover, for both types of TOS (neurogenic and vascular), the specificity (proportion of true negatives of all healthy cases) and sensitivity (proportion of true positives of all diseased cases) of theses tests are low. Nevertheless, their specificity increases when used in combination[171]. Amongst the most frequently quoted provocative manoeuvres are (see pictures 18 and 19) :

- the Roos test[187], also called elevated arm stress test (EAST)[192], viewed by some as the most reliable provocative manoeuvre for eliciting the neurogenic TOS[192], praised for is usefulness in demonstrating the functional ability of the upper extremities[171], it is also believed to stress all three compression sites of the thoracic outlet (scalene triangle, costoclavicular test and axillary space). The patient is asked to hold arm elevation at 90°

* the research of hyperlaxity is not further documented and the authors rather note that motion restriction is frequently reported in the litterature

** Christo et al note that deep tendon reflexes tend to be normal in neurogenic TOS compared to cervical disc syndrome, which aids localise the site of the nervous lesion[192]

of abduction with elbow flexion and to open and close the hands rapidly over a 3 minutes period; the test is considered positive on reproduction of the symptoms[160,192].

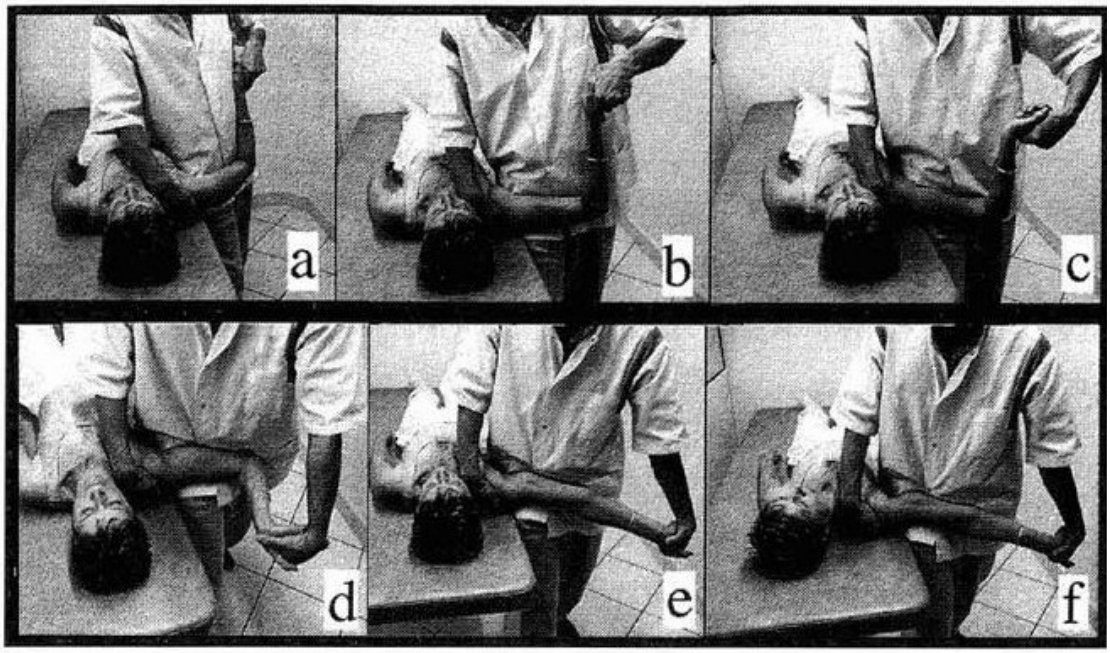
- the Tinel sign performed over the brachial plexus, for a few seconds may reproduce the patient's symptoms[192].Allieu and Amara advise to perform it on all the possible sites of nerve compression[175].

- the Adson's test evaluates the obliteration of the radial pulse while the patient suspends breathing ; because it has many false positives, it is considered poorly reliable[192]

- the hyperabduction test or Wright's test[187] is thought to stretch the neurovascular bundle around the coracoid process. By placing the shoulder hyperabducted to 180° and the elbow flexed. The radial pulse is monitored and the test is considered positive on its obliteration[160].

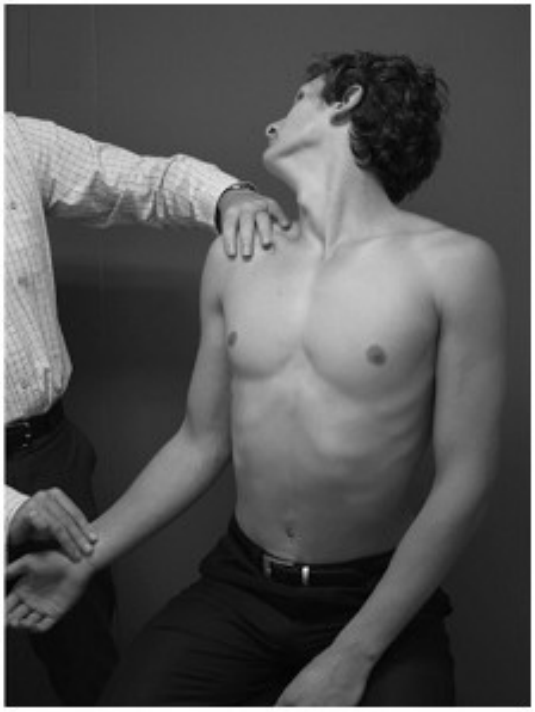
- the Halstead manoeuvre or military test : instructs the patient to assume a military posture which would theoretically narrow the costoclavicular space while the radial pulse is monitored; it is positive on the obliteration of the latter[187,160].

- the Elvey test also called brachial plexus tension test or upper limb tension test or; it has been introduced by Butler and is now often referred to as the upper limb equivalent of the straight leg raise test[179,198]. It is considered as positive on reproduction of the symptoms.



Picture 18 - the Elvey test (upper limb tension test or Brachial plexus tension test) (a) 70° abduction of the upper arm, forearm in neutral position, (b) stabilization of the shoulder and abduction of the shoulder to 110° (c) forearm supination, extension of the wrist and fingers (d) external rotation of the shoulder, (e), extension of the elbow (f) instruction of the patient for active controlateral lateroflexion of the head, reproduced and translated from *Réflexions sur la reeducation du syndrome de la traversée cervico-thoracobrachiale* by Berthe, 2000.

ADSON TEST



HALSTEAD MENOEUVRE

ROOS TEST

WRIGHT'S TEST

Picture 19 - Typical provocative manoeuvres used for the diagnosis of the thoracic outlet syndrome, reproduced from *Thoracic outlet syndrome part 1: clinical manifestations, differenciation and treatment pathways*, by Watson et al., 2009

4.5.3. Complementary diagnostic means for the TOS

Complementary diagnostic means are focussed on the research of the causative factors which have led to the onset of the TOS but also help in the differential diagnosis of the condition (see 4.4.3.). Vanti et al. classify the complementary diagnostic means as either anatomical (plain radiography, computed tomography (CT), magnetic

resonance imaging (MRI), angiography and venography) or physiological (nerve conduction velocities (NCV), electromyography (EMG), Doppler)[171].

Cervical spine and chest X-ray permits to point out degenerative disc diseases, cervical ribs or structural anomalies of the first rib and clavicle[187,197]. MRI and CT permit to image the surroundings of the presumed compression or injury and thus can be used for screening purposes ; they may notably demonstrate bony anomalies, scalene muscle anomalies, cervical disc disease, Pancoast tumour or metastatic involvement[179,187197]. Vascular studies under the form of angiography and venography (which can present an invading character and carry potential risks) should be performed if an aneurysm or thrombus are suspected[180,187]. Electropmyography (EMG) is often considered as not sensitive enough for milder forms of brachial plexus involvement[179,187]. It may show neurogenic damages such as increased motor unit action potential amplitude and/or duration and decreased recruitment at maximum effort[179]. Together with the nerve conduction velocities (NCV) it can exclude other neurologic abnormalities such as radiculopathies, more distal NES (CTS, cubital tunnel syndrome, polyneuropathies and motor neurone diseases[192,197].

Nerve conduction velocity prolongation is seen in patients with longstanding neurogenic TOS; the examination usually focuses on the proximal ulnar and median nerve conduction times[197]; the medial antebrachial cutaneous nerve conduction study has also been identified as sensitive to detect milder neurogenic TOS[154,179,197]. The Doppler, (notably the colour one which is though to have a high sensitivity) is generally indicated for the vascular forms only and permits to assess the patency of the vessels[179]. Some authors question the usefulness of performing such an examination however, due to the fact that the vascular compression is easily detected by the clinical examination[197]. Merle and Borrely for their part argue that its should be systematically performed in order to research any silent vascular complication such as stenosis, poststenotic aneurysm or partial thrombosis before the benignity of such an examination and its high potential in imaging such anomalies[161].Finally, some authors mention the possibility of performing an anterior scalene block; it consists in the direct injection of a local anesthetic agent into the scalene to induce a paralysis of the muscle and a reducition of the pressure and is generally performed under the guidance of imaging methods[187]. This test has emerged as one of the most effective ones for the neurogenic type of TOS and can predict the benefit of a surgical decompression[192].

4.5.4. The differential diagnosis of the thoracic outlet syndrome

"Since TOS has a surplus of funny turns, it may readily masquerade as many other pathologies of the neck, upper extremities or the thorax" [151]. This quotation from Malas and Ozcakar perfectly illustrate the need to differentially diagnose a suspected TOS. Several pathologies can indeed mimic or be mistaken for a TOS : CTS appears the most commonly cited NES that can be confused with TOS, but epicondylitis, complex regional pain syndrome, cervical disc diseases, brachial plexus trauma, rotator cuff pathology and glenohumeral joint instability are other possible candidates to be considered when one present with TOS-alike symptoms[163,164]. It is noteworthy to observe that the TOS is frequently associated with other peripheral mononeuropathies ; Wood and Narakas have found the syndrome to be associated with median nerve compression at the carpal tunnel (respectively in 19% and 31% of the cases), radial nerve compression at the arcade of Frohse (respectively 2% and 15%) and of the cubital nerve at the elbow (respectively 7% and 9%)[199,200]. The exclusion or acknowledgement of these other disorders, necessary for the determination of the therapeutic strategy, requires the systematic performance of specific provocative manoeuvres at the occasion of the clinical examination (for instance Spurling test for cervical radiculopathy)[192] or the conduction of imaging studies, notably electrophysiological ones[163]. Besides ruling out potential mimicking disorders, the differential diagnosis of the TOS should permit to preclude life-threatening afflictions, intrinsically progressive disorders and secondary compression which could be at the origin of the TOS : Pancoast tumour, radiation-induced brachial plexopathy, cyst and any other affliction of the peripheral nervous system in general (multiple mononeuropathies and symmatical polyneuropathies) should be at least envisaged by the examiner[164,175,201].

4.6. Therapeutic strategies proposed for the management of the TOS : physiotherapy, pharmacotherapy and surgery

Treatment options for the NESs are traditionally described as either conservative (i.e. splinting, rest, physiotherapy, pharmacotherapy…) or non-conservative, (i.e. surgery)[6]. This also holds true for the TOS. However in its case, the methods used in

both types of managements are, on top of being varied, recurrently debated, notably regarding the surgical interventions.

4.6.1. The range of pharmacotherapies proposed to TOS sufferers

The pharmacotherapeutic means which can be proposed to TOS sufferers centre primarily on the pain and muscular constraint alleviation[181,192,202]. The are used either a support for conservative measures or postoperatively. Analgetic drugs options range from NSAIDs (to be used with caution because of their side effects on the gastrointestinal tract) to opiods, including local scalene block injections[181,192]. The use of opiods in controlling the pain remains controversial for a variety of disorders and notably for the TOS. Christo et al. however observe than it can proposed when the pain persists and the quality of life is impaired despite previous trials of other therapeutic means[192]. Also, tricyclic antidepressants and SRI can provide relief in the case of neuropathic forms of pain[181]. Scalene block injection consists in the monitored administration of steroids, anaesthetic drugs or botulinum toxin type A at the level of the scalene group of muscles and can therefore either have anaesthetic or myorelaxant effects[179,192,202]. The use of botulinum toxin in particular has showed positive outcomes when combined to conservative therapy[179]. Permitting a selective relaxation of the scalene group, the use of botulinum toxin is to be assimilated on a strategic standpoint to the one of myorelaxants during acute exacerbation of the symptoms[181,187]. Added to this is the range of vasoactive drugs which are to be used in the specific case of vascular types of TOS : fibrinolytic agents and antiplatelet agents at the acute stage of the management, and anticoagulants on the long run to prevent recurrence of the symptoms preoperatively[203].

4.6.2. The physiotherapy as a conservative or post-operative management of the TOS

Contradictorily, even if some surgeons remain dubious as for the efficacy of the conservative management of the TOS[161], the physiotherapy is considered on a consensual manner as the first step in the management of this disorder. Algorithms for the management of TOS traditionally advocate a trial of physiotherapy (provided the

absence of acute vascular impairment for the vascular type or progressive muscle atrophy for the neurogenic type)[160,163,171,202] prior to a surgical management in case of failure or poor results[169,187]. However, since the first set of standardized exercises proposed in 1956 by Peet et al. at the Mayo clinic for the treatment of the TOS, a variety of physiotherapy programs have been released[198]. These different protocols can diverge in more or less significant ways and in nearly all the parameters of a physiotherapeutic management: key points of the initial examination, therapeutic strategies employed, frequency of the sessions, duration of the overall treatment and rates of positive outcomes. Sometimes more drastically, the conceptualization and approach of the disorder appears different and the protocols achieve a more or less national or international reputation. As a case in point, many French leading authors in the field of TOS consider the distinction between what they term as compressive or entrapping types (roughly acute and poorly symptomatic versus more chronic and highly symptomatic states) as a key point in addressing the management of TOS[161,168,198]. Conversely, the English literature seldom makes this distinction.

In 2007, Vanti and colleagues endeavoured to review existing protocols of conservative treatments for the TOS and their efficacy[171]. In this regard, Orset had previously stated in 2000 that: *"an analysis of their results [NB: of diverse protocols of conservative therapy] and in particular their comparative analysis would naturally be erroneous because of the diversity of protocols and evaluation criteria"*[168]. As foreseen by Orset, Vanti et al. found themselves confronted with the difficulty of such a task. They first noticed the disparities and shortcomings of the available studies in terms of level of evidence: smallness of the study samples, undefined inclusion and exclusion criteria of the patients (one has to remember that the diagnosis of neurogenic TOS cannot be objectivised in an overwhelming majority of cases and these patients, for lack of any better, are categorised as 'unspecified neurogenic TOS' sufferers), undefined severity, acuteness or chronicity of the disorder and ambiguity as for the outcomes definition were found to considerably restrict the possibility of drawing any definitive conclusion. However, their review allows appreciating different trends and concepts existing for the physiotherapeutic management of the TOS. As observed earlier, the approach and conceptualisation of etiological factors differs from rehabilitations teams to another. Some emphasise the need for shoulder posture correction by strengthening the shoulder girdle's weak muscles, or to the contrary by stretching or relaxing the

overused muscles; others more globally address TOS patients with a muscle imbalance management or postural correction (more or less centred on the thorax and shoulder girdle) approach. Predominantly mechanical approaches (emphasising joint mobilisations of the cervico-thoracic, sterno-clavicular, acromio-clavicular, and costo-transverse joints) have also been proposed and more recently, protocols regarding neurodynamic disturbances as an essential component of the syndrome have been prescribed. In regards to the therapeutic means, the range of offered therapies is also large, amongst them we can quote : muscle strengthening, stretching, post isometric relaxation (focussing on the shoulder girdle, upper thorax and cervical regions but in various combinations and sometimes with conflicting views as to the muscles to be strengthened or relaxed), joint mobilisations (distally from the thoracic outlet, or on its the delimitating joints, the latter option remaining more controversial), nerve gliding exercises, breathing exercises, taping, adhesive elastic bandages, braces, massage, physical therapy procedures (moist heat, TENS)….That being said, the study of Vanti et all found several points of accordance, i.e. general recommendations on which most authors agree; it is presented in the table 14.

From another angle, it is interesting to notice that several authors outline the importance of a complementation by preventive measures with a view to eliminate or correct identified risk factors; the preventive measures include lifestyle modifications, use of orthesis and adjustment of the working environment[181,164]. Lifestyle modifications would target the posture (during dynamic and static activities), the daily activities (minimizing repetitive motion, overhead work, weightlifting,), and the physical activities choices *("directed towards improved range of motion and flexibility"*)[181]. Laulan et al. outline the necessity of eradicating work-related risk factors and advocate workplace prevention measures[164]. Weiss and Colleague add to this the necessity for TOS sufferers to avoid cold and traumatic factors (for instance carrying skisver the shoulder)[203].

Finally, Wischuck and colleagues are some amongst the few authors[205] to have described a post-operative physiotherapeutic management of the TOS[204]; although they specify that their protocol applies for scalenectomy and neurolysis and that it should be modified in case of first rib resection, they determined key features of such a management: in the acute state, active and assisted active range of motion training (cervical spine, shoulder girdle), scar massage, scar desensitization, scar phonophoresis,

then progressively upgraded strengthening exercises, ergonomic training and work-simulated activities. They also note, along with other authors dealing with this topic, that encouraging the patient to perform previously restricted activities (within the range of pain and gradually) was beneficial, and that exercises should be performed in the positions that cause the least discomfort, in a slow, controlled fashion. Hooper et al. note in an extensive review about the management of TOS that post-srgical physiotherapy should also endeavour to correct postural abnormalities or muscle imbalances is these are found to help prevent a reoccurrence of the patient's symptoms[205].

PATIENT'S ASSESSMENT	- necessity to obtain an accurate history to identify onset, characteristics and evolution of symptoms, disability and social participation problems over time.
	- necessity to perform an accurate physical examination to identify all anatomical and functional sources of compression/entrapment and to exclude or identify other pathologies
	- necessity to identify psycho-emotional factors and factors related to workers compensation claims which can affect disability
PATIENT'S MANAGEMENT	- early activation of conservative treatment in order to address the above factors as soon as possible and facilitate early return to work
	- active treatment strategy composed of information, education, correction of posture and positions at home, at work and at night, daily home exercises, simulation of daily living activities, breathing exercises and general aerobic exercises.
	- adaptation of treatment to individual syndrome characteristics with a "patient centred approach" considering the specific sites of compression, muscular and neurodynamic dysfunctions and daily self management at work, at home and during recreational activities
	- the treatment sessions are preferably not scheduled daily but 1 to 3 times weakly at the beginning of the treatment and 1 to 2 sessions monthly at the end of treatment. This helps to contain costs and facilitates the learning process
	In more sever cases, orthesis, taping, and adhesive elastic bandages or physical modalities (moist heat, TENS, ultrasound) can be used but these procedures must not substitute the active exercises and the correction of posture and muscle imbalances
	- consider the positive and negative prognosis factors, emphasise the positive factors such as patient compliance and intervene when possible in the negative factors (obesity, psycho-emotional factors and problems at work)
	- schedule vocational consultation, work hardening and work place modifications interventions
	- it is helpful if the patient is managed by a coordinated team composed of a surgeon, neurologist and physiotherapist, with possible advice from a psychologist or psychiatrist in cases of severe or chronic pain and from an occupational therapist or vocational consultant in order to facilitate return at work.

Table 14: Consensual recommendations for the physiotherapeutic conservative management of the thoracic outlet syndrome, reproduced from *Conservative treatment of thoracic outlet syndrome, a review of the literature*, by Vanti et al., 2007.

4.6.3. The different surgical approaches available for the decompression in the thoracic outlet

Surgical decompression is traditionally prescribed for the management of NESs when conservative measures have failed or are considered insufficient[6]. In the case of the CTS for instance, the surgical management consists in the transverse carpal ligament division and the release is performed either with a standard open or endoscopic approach[150,194]. In the case of the TOS however, the surgical options appear far more numerous and resort to this management is far more controversial, notably in the case of the neurogenic type[205]. Hopper et al. note that the surgical management is however particularly indicated for the vascular forms of TOS, because of limb-threatening (and also life threatening) complications that can result from arterial or venous compromise. Logically, the goal of such a management is to relieve the mechanical load, hence reduce any of the bony or soft tissue structures contributing to the compression[205].

Retracing the history of the TOS's surgical management, Atasoy recounts the different procedures which have been proposed for the thoracic outlet decompression; the first rib resection was performed in 1861 by Coote, the first rib resection by Murphy in 1908 followed by the first scalenectomy by Adson and Coffey in 1927 and the first claviculectomy by Lord in 1953 (regarding the latter, Atasoy observes that is was a *"rather disfiguring operation"* that never gained popularity). Theses different procedures, chosen on an etiological basis have been further refined over the last century notably regarding their anatomical approaches: posterior, supraclavicular and infraclavicular, transaxillary, transcervical anterior or combined transcervical and transaxillary[158].

Nowadays, three or four of these approaches are classically used by surgeons : the transaxillary, supraclavicular, infraclavicular and posterior surgical approaches (supraclavicular and infraclavicular are sometimes combined) [155,203]. Their preference over another is function of the familiarity of the surgeons with these techniques and of the aetiology and type of TOS which has been identified[203]. Besides, first rib resection, cervical rib resection, scalenectomy are indicated differently according to the objective pathological findings ascertained on the patients[154].

4.7. Outcomes of treatment and prognosis

In their 2007 article reviewing major conservative protocols of treatments (from the first published by Peet in 1956 to the one of Novak et al. in 1995, including the one of Sällström et al. in 1993), Vanti et al.[171] found positive outcomes ranging from 76% to 100% at short term follow-up (14 month) and 59% to 88% at medium to long-term follow-up (after at least 1 year). However, the very definition of outcomes and their measurement varied sometimes drastically according to authors. Vanti and colleagues noticed a multiplicity of qualifying terms of poorly defined meaning (e.g. "poor", or "excellent", left to the subjective appreciation of the patient for instance), of vague limits and more or less targeted nature (e.g. disability results, social participation improvement or worsening). Moreover, the follow-up of participating patients was varying in terms of adequateness from very short term (right after the treatment) to long term (4 years after). The protocols themselves were either very standardized or adapted to patients and data regarding the duration, history and types of symptoms were often lacking. Vanti and colleagues also endeavoured to summarize factors of positive and negative outcomes alleged by the authors of these conservative protocols. Overall the factors of positive outcomes would comprehend according to this review the compliance to an home exercise programme (almost unanimously underlined by the different authors), and the modification of behaviour patterns at home and work; on the other hand, factors of negative outcomes would comprehend obesity, double crush syndrome, prior trauma, severity of symptoms and psychosocial factors (compensation claims and psycho-emotional disturbances). Already in 2000, Orset was outlining what he was thinking to be some key factors in the quality of the results reachable through conservative management: the initial severity of the symptoms, the progression of the disease, the time lapse before the beginning of the treatment, the adaptation of the techniques to the syndrome's type and the patient's motivation and compliance[168].

In a retrospective study of Ghoussoub et al.[88] about the predictive factors of outcomes in the rehabilitation for TOS and concomitant to the one of Vanti et al[*]., others determiners of good or poor prognosis were put forward. Factors of positive outcomes comprehended the alleviation of parasthesia and a negative Tinel sign on the brachial plexus right after the sessions. Factors of negative outcomes on the other hand

[*] but which was not included in the review of the latter

included sensitive disturbances and a positive Adson's at the moment of the diagnosis, and a background of "hyperlaxité ligamentaire", (i.e. hypermobility, the direct translation of the term being poorly used in the French literature). About the latter, they determined that hypermobile patients showed an improvement at the beginning of their management regarding the muscle contractures and the compressive phenomenons at play. However, according to the authors as the hypermobility persists, the muscle strengthening provided by the exercises they proposed remained delayed and the proprioceptive exercises efficiency was decreased compared to the other patients. The authors noticed that the amelioration of their state on a long-term basis was undeniable but less (*"not enough"*) than for non-hypermobilie patients. Yet, as the compliance to the home exercise program was the same for non-hypermobile and hypermobile patients, Ghoussoub et al. noticed that the recurrence rate of TOS was the same in hypermobile and non-hypermobile patients. Thus for these authors, hypermobility would be a factor of lesser outcomes in the management but not of recurrence of TOS. It has to be noticed that the rehabilitation in this study was performed on a mean range of 11 sessions and according to the principle of Revel et al. which is frequently quoted in the targeted French literature and centred on the treatment of the cervicalgia, strengthening of the opening and relaxation of the closing muscles of the costoclavicular space (massage, stretching, strengthening exercises combined with diaphragmatic breathing)[88,168,198*]. Patients were further instructed to perform home exercises for at least a year after the termination of the management and 69% of the patients were considered to reach an overall long-term improvement.

Regarding the surgical management of the TOS, the frequency of positive results varies extremely from 24% to 100%, claimed Lindgren[206] in 1995. The major complication seems to be the regeneration of fibrocartilage and new bone by a remnant rib left during the surgery. Other risks include: nerve injuries of the brachial plexus, of the phrenic nerve, of the long thoracic nerve and the recurrent laryngeal nerve, Horner's syndrome (ipsilateral deficiency of the sympathetic activity)[154,182]. In 1995, reexamining 45 cases of TOS surgeries (transaxillary first rib resection mainly and cervical cervical rib resection), Lindgren[207] outlined several findings which could explain poor outcomes: (multiple) cervical anomalies, CTS, fibrositis, cervical spondylosis vibration neuropathy amongst others. In 2004, Degeorges et al.[208] found that acute ischemia at the time prior

[*] according to these publications, no proprioception-centered exercises is included in the protocol of Revel et al.

to the operation, sensory or motor deficit, poorly systematized neurological symptoms as presenting symptoms, extended resection of the first rib and severe postoperative complications were constituting factors of poor outcomes in the surgical management of the TOS by partial or complete first rib resection.

5. Findings

The following chapter summarizes the relevant facts which were recollected in the previous sections of this work, with regards to the connection between the HMS and NES, more specifically the TOS. It aims at merging evidence and information which have been gathered about these disorders in order to answer to the investigative questions stated in the first pages of this thesis. All statements are referenced previously in the corresponding chapters of this literature review.

5.1. Overview of the connectedness between hypermobility and nerve entrapment syndromes.

In the actual state of the scientific research, joint hypermobility and its pathological expression, the HMS, both constitute an etiologic, nosologic, diagnostic, and clinical conundrum. Etiologic and nosologic first, for their actual genetic basis, although ascertained, remains obscure; indeed, unlike its most malevolent hereditary kins _the Marfan syndrome, osteogenesis imperfecta and some subtypes of Ehlers Danlos syndrome _, which all share the common feature of hypermobility, the HMS is reputed benign before the absence of incidental life-threatening disorders. Accordingly, it is considered as an attenuated form of an heritable disorder of connective tissue. But this status of hereditary disorder, again, undeniable as the syndrome shows an autosomal dominant inheritance pattern, has yet not been confirmed by the identification of a genetic defect or protein insufficiency. In the absence of available laboratory examinations and because of their similar features, the condition is merged with an previously distinct other HDCT: the EDS-HT, rendering an actual classification impossible. As a result of this etiological enigma, the diagnosis of hypermobility or hypermobility syndrome solely rests upon the clinical examination. Two tests, which have proven to be of satisfactory validity and reliability, are most commonly used, notably for research purposes: the Brighton criteria for generalized joint hypermobility and the Beighton criteria for the hypermobility syndrome. But despite their fastness and easiness of performance, their execution on patients difficulty goes over the sole research setting. Investigations conducted in the United Kingdom have shown that hypermobility in general was underdiagnosed and overlooked despite being appraised

as the most common motive of consultation for rheumatological disorders. Besides, the clinical presentation of HMS is not outdone in terms of complexity. The actual understanding of the disorder is that its manifestations are predominantly rheumatologic, possibly widespread and etiologically associated with variable impairment of nearly all organs or systems. Once its has broke out, the syndrome is chiefly characterized by pain, but hypermobility can become symptomatic at any age, in virtually any region of the body, with either an isolated or recurrent character and under extremely variable pathological forms. Moreover, HMS affects patients in different extent and the disability it provokes varies from mild to severe.

The denomination NES on the other hand refers to a broad group of focal lesions of the peripheral nerves resulting from an injury at vulnerable anatomical sites. They share more or less common traits in terms of pathological presentation, etiological and risk factors, pathomechanisms, means of diagnosis and treatment options. The TOS constitutes one the many examples of NESs that have been described in the literature. The syndrome encompasses any compressive impairment of the neurovascular bundle formed by the brachial plexus and the subclaviand and axillary arteries and veins at the level of the cervico-thoraco-axillary space. Two types are classically distinguished: the vascular type accounting for a minority of the TOS sufferers and the neurogenic type which represents the overwhelming majority of the cases. Its aetiology varies from congenital anomalies, to functional factors, including traumatic events. It is mainly diagnosed by clinical examination and the settlement of the diagnosis for a majority of patients lacks objective evidence. The clinical examination which is recommended traditionally implies the performance of several provocative manoeuvres which lack of sensitivity and specificity.

The retrieved studies have permitted to establish that a clinical link exists between this primary rheumatologic disorder which is the HMS and these essentially neurological afflictions which are the NES. Indeed, between 1987 and 2013, it appears that 12 publications (case reports, prospective (controlled) studies, comparative studies and prospective controlled trials) linking in some way NES to JH/HMS/EDS-HT were released in the scientific literature. Their analysis has permitted to take stock of this connection, which is incidentally poorly mentioned in monographies[18,104] treating about HMS :

- about the types of NES which can be seen concomitantly with HMS: overall, HMS has been correlated with seven different NESs of the upper as well as of the lower limb: the TOS/brachial plexus palsy, the ulnar nerve entrapment, the CTS, the digital nerve compression, the sciatica, the CPNP and the TTS. Additionally, symptoms suggestive of peripheral nerve involvement were also reported by some authors : acroparesthesia in 57,9% of the 114 HMS patients in the study by El-Shahaly et al.[70] and in the totality of the 7 patients affected by CTS and HMS in the cases reports of Rovetta et al. [84], sensory and/or motor disturbances of the upper limb in 54% of the 378 HMS patients in the study of Hudson et al. [87] and upper or lower limb paresthesia and muscle cramps in respectively 80%, 20% and 86,7% of the 15 EDS-T patients in the study of Granata et al. [91] Overall, the CTS appears as the main type of NES from which HMS patients can suffer.

- about the general impairment of the peripheral nervous system in HMS patients : two studies noted the simultaneous and/or repeated occurrence of different NES in hypermobile patients. Coexistence of CTS and TTS in 14% of the patients in the El-Shahaly et al.'s study[70], coexistence of sciatica, and bilateral CPNP in the patient reported by March et al. [82] and consecutive brachial plexus palsies and lumbosacral palsies in the patient reported by Galan et al. [86]

- about the likeliness for NES sufferers to present hypermobility and vice versa: according to the angle from which was tackled this correlation (HMS-centred study or NES-centred study), the NESs were detected at higher rates than the norms in HMS patients or the HMS was found in significant proportions of the NES patients' sample. Thus, in the study of El-Shahaly et al. [70], 61,6% of the HMS patients were presenting a CTS and 14% of the HMS patients were presenting a TTS; in the study of Hudson et al.[87], 26% of the HMS patients were diagnosed with TOS. Conversely, in the study of Francis et al. [81] 81% of the TTS suffers were found to have hypermobility, and in the study of Ghossoub et al[88], 42,5% of the TOS sufferers were found to have ligamentous hypermobility. In the study of Aktas et al. [89], 85% of the CTS patients were found to have HMS.

Overall, there exists bidirectional evidence regarding the connection of HMS and some types of NES. This link has been investigated and/or reported for the TOS/brachial plexus palsy, the ulnar nerve entrapment, the CTS, the digital nerve compression, the sciatica, the CPNP and the TTS. Authors of these publications reported either higher prevalence of NES than expected in the HMS patients or high

rates of clinical hypermobility in their NESs patients. The CTS constitutes the NES for which the evidence of its correlation with HMS is the most documented as it was reported in 5 of these 12 different studies and on the biggest number of patients. It correlates with its status of most common type of NES encountered in the general population. TOS comes second equally with TTS as they have been reported in 2 of these 12 different studies. Moreover, there is evidence for arguing that HMS suffers are at risk for developing NES (at least those investigated types) on an isolated manner at one site, on a plural manner at different sites at the same time or on a reiterative manner at different sites and at intervals between their respective onsets.

5.2. Possible pathological mechanisms for the onset of nerve entrapment syndromes within the framework of an underlying hypermobility/hypermobliity syndrome

The actual conception of the connection between NES and JH is that the latter would act as a predisposing/causative factors for the onset of NES: NES would develop in a background of pre-existing hypermobility; the latter would become at this occasion symptomatic (because of the onset of NES) or could have turned out to be symptomatic before, because of another rheumatologic complaint for instance. Consequently, the patient would present not just coexisting NES and hypermobility but rather a HMS. This logic of NES caused by a pre-existing JH/HMS pertains to the factual knowledge available for both syndromes. On one hand the onset of NES is very unlikely during childhood or adolescence (e.g. traditionally between 20 and 50 years old for a majority of TOS sufferers). On the other hand, (i) Hakim et al[23]. have demonstrated that hypermobility is at 70% innate, (ii) HMS is considered as a genetic condition of autosomic dominant inheritance pattern, (iii) it is nowadays considered as an HDCT (similar to EDS-HT); accordingly, it can be qualified as pre-existing. The causative/predisposing character of JH for the onset of NES is incidentally stated as such in the monographies[18,104] retrieved about HMS.

Some authors of the same aforementioned publications[70, 81-91] have attempted to theorise the link that they observed between different types of NESs and the HMS. By the synthesis of their writings, it appears that the hypermobility could negatively impact the peripheral nervous system in two different (and probably combined) ways :

- poor resistance to the mechanical factors exerted on the peripheral nerves because of the poor quality of connective tissues
- increased mechanical forces exerted on the peripheral nerves because of (i) the possibility for hypermobile patients to perform static and dynamic postural activities beyond the physiological norms of ROM (ii) sequelar orthopedic anomalies imputable to the poor quality of the connective tissues in HMS patients

5.2.1. Increased intrinsic vulnerability of peripheral nerves to mechanical factors

In a 1990 publication of case reports, Rovetta et al. [84] hypothesised that in the case of CTS, the hypermobile patients would present an increased aptitude to produce a subclinical (i.e. non-detectable by traditional imaging means) oedema. The latter would result in the compression of the median nerve. Voermans et al. [90] in 2009 argued that the extracellular matrix defect seen in HDCTs affects also the peripheral nervous tissue. In the most recent study retrieved, Granata et al. [91] correlated a high rate of ulnar nerve subluxations and luxations to a possible hyperlaxity of the Osbourne ligament. The latter would, according to them enhance the frequency of ulnar nerve luxation and subluxation at the elbow which would eventually cause recurrent friction between the nerve and the bone. Before the complex relationships between altered connective tissues and nerve, they retained from hypothesise about the pathological mechanisms at play in case of coexisting HMS and NES.

However, the anatomical structure of peripheral nerves, their mechanical properties and the pathological mechanisms at play at the occasion of their involvement in NES is nowadays well known. Nerves fibres are embedded in different protective layers of connective tissues (perineurium, endoneurium and epineurium) and endowed with a vascular and nervous support system. They are furthermore sporadically fixed to adjacent connective tissues by a mesoneurium. Because of (i) the intrinsic qualities of these different sheaths of connective tissues, and (ii) the arrangement of the nerve fibres and fascicles provided by collagen fibrils networks of the latter, the peripheral nerve trunks are well designed to sustain mechanical forces (strain and compression) physiologically exerted during movement. Because of the blood-nerve barrier provided by the perineurium, they are also resistant to toxins.

Nerve injury seen in NES can be categorized in its least severe form as neurapxia (temporary loss of function, no neural disruption) or more severe as axonotmesis (axonal and myelin sheath disruption with connective tissue sheath preserved). The nerve injury observed in NES it is thought to result mainly from a mechanism of compression. At an acute stage, the nerve compression would provoke a cascade of ischemia, inflammation, oedema, to result in decrease in the axon function. If chronical, the compression causes a persistent endoneuroal oedema leading to intraneural fibrosis, axon and myelin changes, and ultimately perineural thickening. Concomitantly, the structure of the myelin sheath of the involved nerve fibres is thought to be subjected to pathological changes, making the nervous tissue more vulnerable to previously innocuous stimuli such as higher levels of adrenaline produced during stress for instance. Other mechanisms of injury have been described, notably traction (i.e. strain) for the upper limb NES. According to the kind and strength of traction, the duration of the traction and the topographical location within the nerve, the traction can impact more or less severely the peripheral nerves: from impairment of the intraeural circulation to impairment of the axonal function and intraneural scarring. Finally, the double crush syndrome constitutes a third pathological mechanism explaining the onset of not one but two (or sometimes more) NES in the same individual. This theory argues that a proximal site of compression on a peripheral nerve renders its more distal portions less tolerant to compressive force and thus more likely to be injured. Considering the fact that in some of the aforementioned studies, HMS suffers were found to present simulatenous or conscutive NESs, the theory of the double crush mechanism appears coherent.

In the light of what has been said; it is possible to complete the hypothesis exposed at the beginning of this section: The endoneurium, perineurium, epineurium and mesoneurium would not be as resistant to strain and compression in hypermobile individuals as they are physiologically supposed to be. However, the extent and nature of their impairment cannot be ascertained, for no actual protein or genetic defect has been found yet in HMS sufferers and as nerve tissue structure cannot be assessed without patent risk of damages; it indeed requires nerve biopsy which is traditionally avoided because of its risk and nerve tissue integrity is generally assessed only by its function. As a result of the latter, this pathological mechanism remains purely theoretical.

5.2.2. Increased mechanical constraints caused by postures.

March et al. [82] gave two examples of postures (sleeping and lotus position) which they incriminated for the onset of NESs in their patients (CTS and CPNP and sciatica respectively). These postures were either took on easily only by hypermobile patients or performed in ranges only reachable by hypermobile individuals. In the case of the CTS, it was the range of wrist flexion attainable by the patients and their sustainment throughout the night that was argued to cause the syndrome. This mechanism was later reprised by Aktas et al. [89] who found night paresthesia in a majority of their patients who presenting both hypermobility and NES.

Considering the postural issue in the NES-JH/HMS correlation, let us analyse the problem according to two different standpoints :

- firstly the one of the hypermobility: Booshanam et al.[106] found that HMS patients were presenting significant deviations of their standing posture towards the norm (head, hip, upper back, trunk and lower back). They explained these deviations by the adaptation to pain (which they put forward as the initiating factor for most of the postural deviations), and sequelae of the capsuloligamental laxity exerted by HMS patients. Galli et al. in 2011[123], Rombaut et al. in 2011[124] and Rigoldi et al. in 2012[111] examined for their part the gait of HMS patients and found it to be also non-physiological. It emerges from their findings that gait is impaired in HMS patients as a result of a combination of hypotonia, muscle weakness, compensatory mechanism and fatigue. It remains unclear for the aforementioned authors whether these abnormal postures are the result of initial microtrauma impairing the proprioception or rather initial defective proprioception causing microtrauma and Booshanam[106] merely settled for a vicious circle of decerased stabilizing function, proprioceptive loss and postural deviation. Bergmark[127] for his part argues that hypermobile individuals frequently overuse the global muscle system and have difficulty recruiting the local postural system.
- secondly the one of the NES: analysing possible etiological factors involved in the onset of NES (particularly TOS), Novak et al[170]. have theorised about how incorrect postures impact the nerve trunks and plexuses. For them, static or dynamic positions of the head, neck and upper limbs, assumed at work or during sleep can (i) directly increase the pressure on nerve entrapment sites, (ii) result in the adaptative shortening of some muscles which also can compression the nerves and (iii) result in adaptative

elongation and weakness of other muscles. This would cause the overuse of some muscles and overall start a cycle of muscle imbalances, fixating the postural defects.

In conclusion, HMS patients on one hand present defective postures, and on the other hand are able (because of their "flexibility") to take on exacerbated others. Yet incorrect posture can directly result in nerve compression at anatomical bottlenecks or indirectly trigger muscles adaptative shortening, elongation and imbalances which also give rise to nerve compression or tension. Thus, in NES, posture represents a main *causative* issue; particularly in TOS, it is ascertained as one of the main factors for the onset of the syndrome and is consequently generally tackled in rehabilitation programs. In HMS, however posture represents a *resultant* issue. Its rehabilitative approach is by education for transiently adopted deleterious postures and by classical rehabilitation when postural deviations are settled.

5.2.3. Increased mechanical constraints caused by orthopaedic anomalies

NES are overall the doing of a mechanical constraint exerted at anatomical bottlenecks, namely inextensible anatomical paths which can consist in osteofibrous tunnels, osteomuscular tunnels or fibromuscular tunnels. For the TTS, Francis et al. argued that sequelae of hypermobility under the form of mobile flat feet and hindfoot valgus were to be incriminated in the stretch of the tibial nerve in the tarsal tunnel and its subsequent injury. For the TOS, Hudson et al.[87] stated that ligamentous laxity could be an important factor in the anatomical changes resulting in a pressure phenomenon of the thoracic outlet.

Mild orthopaedic anomalies are frequently found in HMS sufferers; amongst them we can quote (not exhaustively) dorsal hyperkyphosis, lumbar hyperkyphosis, scoliosis of mild degrees, cubitus valgus, genu valgum, flexible flatfoot, hallux valgus… Castori[3] explains that because of the congenital capsuloligamentous laxity which characterises individuals exhibiting hypermobility, the late stages of morphogenesis can be negatively impacted and give rise to orthopaedic anomalies. According to him, the moulding of the skeleton is indeed more impacted by mechanical stimuli (gravity, muscle contraction…) on such individuals because of the poor resistance of capsuloligemental structures to these constraints.

Thus, because of its propensity to cause orthopaedic anomalies, hypermobility can further cause narrowing of some of the vulnerable anatomical sites through which nerve trunks and plexus travel. The ensuant narrowing eventually impairs the nervous structures, causing a NES.

5.3. Possible consequences on the therapeutic management of nerve entrapment syndromes

The NES are classically managed conservatively (pharmacotherapy and physiotherapy) and/or non-conservatively (surgery). In the case of the TOS syndrome pharmacotherapeutic means are primarily directed toward pain control and muscular constraint alleviation. In this regards, analgesics ranging from NSAIDS to ultimately opioids, can be used and tricyclic antidepressants and SRI constitute a last resort in case of neuropathic form of pain. Myorelaxants and alike medications can be systemic or, with the injection of botulinum toxin, ca be targeted towards the selective inhibition of the scalene muscle group. The surgery of the TOS is done according to three of four mains approaches (transaxillary, supraclavicular, infraclavicular and posterior) and aims at decompressing the neurovascular bundle in the thoracic outlet mainly by first rib resection, scalectomy, or cervical rib resection if present.

Yet when it comes to hypermobile patients, who classically face the same pharmacotherapeutic options that those given for NES patients (analgesic drugs and myorelaxant notably), Grahame[28], Castori[3] and others note that their employment can prove to be counter-productive, because of the exacerbation of their adverse effect. They note that myorelaxant may cause the amplification of joint instability, multiple dislocation and consequent exacerbation of pain and fatigue. Regarding analgesic drugs, they advocate acetylsalicylic acid to be rule out, as its antiplatelet action increases the tendency to haemorrhages and ecchymoses, which is already important in HMS patients because of the tissue's fragility. Lastly, they note that steroid injections (a commonly performed treatment for CTS for instance) tend to inhibit the collagen synthesis by fibroblasts, and consequently their use present an adverse effect on the tensile strength of already intrinsically collagen rich yet weakened tissues. Regarding the effectiveness of surgical procedures in hypermobile individuals, Rombaut et al.[128] determined that a

large proportion of non-conservative procedures prove to be inefficient or with lesser outcomes than expected (33,9% only of favourable outcomes). Factors of negative outcomes for surgery in hypermobile patients have been outlined as: the friability of tissues, possible difficulties of homeostasis, delayed/incomplete healing, scarring issues and wound dehiscence.

Regarding the physiotherapeutic options available for TOS sufferers, many different conservative protocols with more or less positive outcomes have been proposed over the last 60 years. In their approach and conceptualisation of the etiological factors to be acted upon, these protocols differ sometimes quite importantly. Their actual comparison in terms of effectiveness appears impossible due to their variety, the difference of outcomes measures, the criteria of patient's inclusion, the durations of the treatment protocols and the disparities in the level of evidence notably. Several trends in terms of treatment goals and means can however be outlined. Regarding the goals, current trends in treatment focus notably on the patient's assessment (history, physical examination, psycho-emotional factors), an early activation of physiotherapy, and advocate a patient-centred approach. Physiotherapeutic means encompass notably muscle strengthening, stretching, post isometric relaxation, joint mobilisations, nerve gliding exercises, breathing exercises, taping, adhesive elastic bandages, braces, massage, physical therapy procedures. Patient's education holds a preponderant role in the management of the disease. Several factors of positive or negative outcomes in the management of the TOS have been outlined by different author; regarding the former: compliance to an home exercise programme and the modification of behaviour patterns at home and work would be important hkey to successful management of TOS sufferers; regarding the latter, obesity, double crush syndrome, prior trauma, severity of symptoms and psychosocial factors would have a negative impact on the management of TOS sufferers.

One study about TOS showed that on top of acting as a predisposing or causative factor for the onset of NESs, the hypermobility (syndrome) acts a negative factor of outcome in the physiotherapeutic management of at least one type of NES: the TOS. As a matter of fact, it was the only study that could be retrieved regarding a NES management and which outlined first an underlying hypermobility in some of the patients and second a possible role it played on their management; In this study by Ghossoub et al.[88] identified hypermobility as factor of negative outcome and determined

that hypermobile patients showed a similar improvement (in terms of time and extent) regarding muscle contractures and compressive phenomenons but a delayed and lesser improvement in terms of muscle strengthening. The hypermobility was however not constituting a factor for the recurrence of the symptoms.

Thus it appears that treatment options, whether they are pharmacological, physiotherapeutic or surgical are lesser for hypermobile patients. Regarding the conservative management of TOS, hypermobility constitutes a factor of delayed outcomes in terms of muscle reconditioning but not in terms of recurrence of the symptoms.

6. Discussion

In this chapter will be reviewed the aforementioned findings in a critical and subjective manner : the level of evidence of the studies linking HMS and NES will be discussed and personal comments will be made on the different issues that are raised by such a correlation.

6.1. About the level of evidence regarding the correlation between hypermobility and hypermobility and nerve entrapment syndromes

The overall level of evidence regarding the connectedness between HMS and NES remains unsatisfactory. However, as mentioned earlier, HMS-centred reference monographies[18,104] seem to "turn their nose up" at this fact and, quoting cases studies or prospective studies, they argue that hypermobility can lead to the onset of NES. In this regard, it seems that their statements could be considered rather as "expert opinions" than as scientifically evidenced facts. Yet this literary review focusing on this very same connection suffers from analogous weaknesses first pertaining to the characteristics of the published literature on both topics :

- firstly, the literature documenting JH/HMS to NES (specifically or incidentally) is extremely scarce. The methodology used for this work has allowed retrieving only a dozen of case reports and studies dealing about the two syndromes. In like manner, the same observation is done by several authors, notably those of the aforementioned monographies[18,104] who don't go without deploring it.
- secondarily, the types of publications retrieved and correlating HMS and NES are characterized by their poor level of evidence : 5 cases studies about 1 (Bell et al.[85], Patrone et al. [83]) 2 (Gallan et al. [86]), 4 (March et al. [82]) or 7 (Rovetta et al. [84]) patients, 6 prospective studies including 3 controlled ones and only one comparative study. Consequently, it seems logical to remain dubious about the actuality of the correlation between certain NES and HMS, for instance notably in the case of digital nerve compression as it has been documented solely by Patrone et al.[83]
- thirdly, even if we do not consider the case reports, several of these studies were characterised by the smallness of their study samples. As an example, the prospective

study published by Francis et al.[81] about the correlation between TTS and JH included only 9 patients. Yet this study is frequently quoted (38 quotations according to google scholar) by authors who notably endeavour to expose the etiological factors of this NES. One can ask oneself : is it so for lack of any better evidence ? Or do these authors consider that this evidence is sufficient ?

- fourthly, the recognition of patients as affected by some types of NES lacks diagnostic rigour, particularly in the prospective studies dealing primarily with HSM. In this regard, the thoroughness of this literary review has given us key points to bear a critical view on the assessment of one's NES's actuality. As we explained earlier in this review, the diagnosis of NESs follows overall the same process: clinical examination, performance of provocative manoeuvres and confirmation by clinical imaging means. However, in the case of the TOS, the provocative manoeuvres lack of sensibility and specificity. One of the most commonly performed provocative manoeuvre, the Adson's test for instance is frequently found positive in an normal population. Accordingly one can wonder about the actuality of the TOS cases diagnosed by Hudson et al.[87] in their hypermobile patients; they recall performing a single Roos manoeuvre, not complemented by any other provocative manoeuvre (although this enables increasing the specificity of the diagnosis) for settling the diagnosis of TOS. Conversely, it can be the diagnosis of HMS which can be questioned in other studies, for instance, in the study of Ghoussoub et al.[88], although the star finding of their study is the fact that JH constitutes a negative factor of outcomes in the treatment of TOS, the authors do not describe the diagnostic methods which was employed for the assessment of this hypermobility.

On the other hand, the possible pathological mechanisms advanced by the authors of the aforementioned studies are confined to a theoretical stage. However, they remain coherent with the current *theorised* pathological mechanisms which have been put forward with NES. The study of Voermans et al.[90] appears particularly interesting in this regards, for it attempts to provide a precise histological and functional basis regarding the nervous tissue fragility that could be observed in HMS patients. Yet the authors and their results could end up facing the limitations of the imaging techniques. Indeed, for some NES, and as it is the case for the TOS, the traditional imaging means _nerve conduction velocity and electromyography_ notably remain silent despite a patent symptomatology. It is interesting to notice if Voermans et al.[90] kept from performing nerve biopsy and settled for functionally analysing the integrity of the

nervous tissue (yet the EMG they performed showed anomalies in HMS patients), they didn't go without performing muscle biopsy (less detrimental than nerve biopy) and found structural defects of the muscular tissue in EDS-HT patients. They imputed this structural defect to the extracellular matrix of connective tissue.

6.2. About the issues raised by the correlation between hypermobility and hypermobility syndrome and nerve entrapment syndromes

Several issues and subsequent interrogations arise from observing a predisposing/causative link between hypermobility and the onset of NES:

- first about the very recognition of this causal link: is the medical corps aware of this reality and has taken its full extent ? Now we have already mentioned that NESs were stated as occurring in relation with HMS in few reference monographies[18,104] about the latter syndrome. But what about from the other angle, the one of NESs ? To date, a multitude of aetiological factors have been defined for the latter syndromes: obesity, pregnancy, metabolic diseases, rheumatic diseases, ergonomic factors to quote the most frequently claimed ones. Let's take the case of the CTS for instance for which an almost epidemic metabolic disorder, the diabetes mellitus has been outlined as an etiological factor. An unrestrictive research on Pubmed combining the key words "diabetes" and "carpal tunnel syndrome" retrieves 310 entries; the same research with the word "hypermobility" instead of "diabetes" retrieves… 5 studies (all of them used in this thesis for that matter) ! The result of this little experiment, is to me symptomatic of the under-recognition of this link, at least by these who deal with NES.
- second, about the presumed under-recognition of this link: one can ask oneself how come such a, if not well documented, at least a priori logical link could be overlooked in the actual appreciation of the NESs ? Were does this underrecognition stems from ? Is our topic to young for the medical literature ? Or are there other clues that can explain this state of affairs? According to me, the answer is to be searched around hypermobility rather than NESs, for the former is notably underrecognised by the medical corps. This has been shown by Grahame et al.[54] in 2001 and if any need is of more proof of this underrecognition, here is a little anecdote: when I was doing preliminary researches on the topic of this thesis, I had a look at my "physiotherapy

bible"[209] referencing clinical guidelines for hundreds of conditions a physiotherapist is entitled to treat; the "syndrome d'hypermobilité bénigne" or "hyperlaxité" (the book is in French language and from a 2009 edition) was not even mentioned in it! Logically, as the joint hypermobility is underrecognised (according to Grahame[22,39] because of the erroneous belief that hypermobility represents the upper end of a Gaussian curve distribution of physiological ROMs) the HMS is underdiagnosed. But to me the underdiagnosis of the HMS originates from maybe even more causes: its reputation of benignity, the absence of clear boundaries with another more detrimental syndrome (the EDS), the former definition as mere rheumatological disorder characterized by joint pain, the absence of laboratory means for its diagnosis, the migration of patients who present a variety of diverging complaints and seek for help accordingly with different specialists, the scepticism of the medical corps before those patients who present a multiplicity of symptoms and are taken for hypochondriacs… The latter constitute several facts, documented and still actual, which have been outlined through this thesis. In such circumstances, it seems natural to observe that if one (the HMS) is underrecognised, then the link that unites both (NES and HMS) is missed too. And in such case, doesn't it have consequences in terms of patient's management ?

- thirdly about the clinical consequences of this link's recognition: if joint hypermobility/HMS constitutes a predisposing/causative factor for the onset of NES, shouldn't one try to act on it ? Let's take again the example of a CTS with an underlying diabetes mellitus. In such case, aren't patients presenting both disorders treated accordingly ? Assuredly the endocrinologist in charge of such a patient would make sure that he/she has a controlled blood sugar, at least to prevent any further disablement. Going back to hypermobility, in only one study By Ghossoub et al.[88] it was quoted as impacting negatively the management _physiotherapeutic_ of a NES: the TOS. So definitely it needs to be taken into account in order to improve the outcomes of management.

- fourthly about the clinical consequences of this link: as Ghoussoub et al.[88] have shown, this causal link between hypermobility and NES (in their case the TOS) has clinical repercussion: at least for the TOS, hypermobility plays as a negative factor of outcomes of the physiotherapeutic management of this disorder. Isn't it possible once hypermobility has been recognised to thwart its negative impact on the management of the TOS for instance ? TOS's mainstay of management is physiotherapeutical and so is the one of HMS, so the physiotherapist is so to speak the sole "master and commander"

regarding thoracic outlet compression and hypermobility. One of my most esteemed teachers, a physiotherapist, once told me that it wasn't the recognition of hypermobility that was problematic but rather the possibilities for counteracting it. But is it really so ? There are specific therapeutic strategies adopted for HMS patients: enhancement of the proprioception, core stability training, targeted education. Why not applying them on these patients who both present complaints and hypermobility ? In my opinion and regarding at least the TOS, if hypermobility is detected, it could be beneficial to implement in their management techniques fit for HMS patients, or at least orientate our choice of techniques. Why not for instance choose proprioceptive neuromuscular facilitation rather than stretching or strengthening for the neck muscles imbalances these patients frequently show ? Why not making these patients realise their state of hypermobility and guide them towards a better joint protection ? When attempting to correct postural defects, why focussing only the shoulder girdle as some protocols of treatment for TOS advocate ? Why not performing emphasising knee proprioception in the long-term management to enhance a postural correction for instance ?

7. Conclusion

Hypermobility, HMS and NESs are undeniably related, for the latter are found at higher rate in hypermobile patients when sought for and for their management (at least the one of the TOS) can suffer lesser outcomes when conducted in the presence of to the former. Thus, hypermobility and HMS act as predisposing or causative factors in the onset of several NES, including the most commonly diagnosed one, the CTS but also as negative factors of conservative management in the case of the TOS. However, this link is established by evidence of a poor quality and, what is more, foreseen as underrecognised. In this regard, the partition of this literature review along two main axis involuntarily echoes the (too) neat separation which can be done between the two syndromes; this distinction pertains first to a nosologic matter for the HMS is primarily a rheumatologic condition whereas the NESs rather belong to the domain of the neurology. This state of affairs could also be to blame on the primary poor recognition of hypermobility, and of its pathological expression the hypermobility syndrome. Yet, the first definition provided by Kirk et al. in 1967 has evolved and it is time for medical corps to reckon and deal with the hypermobility syndrome's multifaceted character and almost ubiquitous ability to trigger musculoskeletal disorders.

It appears logical that this correlation, since causal, negatively impacts the management that can be done of NES syndromes, and this has been proven for the TOS conservative management. But more still, the ignorance of this correlation, i.e. the fact of overlooking hypermobility when addressing a case of NES, also could prove to be deleterious. From a pharmacological and surgical standpoint, therapeutic strategies can have counterproductive effects when a patient presents hypermobility. Maybe more importantly, from a physiotherapeutical perspective, the recognition of hypermobility and of the HMS appears crucial; conservative management is indeed the first elective therapy for a variety of NESs. It could appear that in such case, denying the acknowledgement of such a factor or even such a syndrome results in less accurate choice of strategies (therapeutic, but also temporal) for the management of the patient's condition; in other words, being ignorant of the possible correlation between HMS and NES deprives the physiotherapist from a key feature and tool of his profession: the closest tailoring of the treatment goals and strategies to answer the need of his patient, but also prevent further reoccurrence of the condition. To this end, a the probably most

highly anticipated advance in the field of HMS-related researches is the discovery of its underlying genetic defect, which would first make the condition gaining in notoriety and second allow solving a majority if the conundrums arouse by this disorder.

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9. Appendix

Appendix n°1: list of abbreviations

BJHS benign joint hypermobility syndrome

CN: compression neuropathy

CT: computed tomography

CTS : carpal tunnel syndrome

EN: entrapment neuropathy

EDS : Ehlers-Danlos syndrome

EDS-HT : Ehlers-Danlos syndrome hypermobility type

EMG: electromyography

HDTC : heritable disorder of connective tissue

HMS: hypermobility syndrome

JHS : joint hypermobility syndrome

MRI: magnetic resonance imaging

NCV: nerve conduction velocity

NES: nerve entrapment syndrome

NSAID: non-steroideal anti-inflammatory drug

ROM: range of motion

SRI: serotonin reuptake inhibitor

TOS : thoracic outlet syndrome

Appendix n°2: list of illustrations

Appendix n°3: List of tables